



# BULLETIN

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



JANUARY 1946

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CONTRIBUTIONS OF THE WAR EFFORT  
TO MEDICINE

CORNELIUS P. RHODES

Acting President The New York Academy of Medicine

THE subject of this 18th Graduate Fortnight of The New York Academy of Medicine is the Contribution of the War Effort to Medicine. It is apparent from the program that this contribution is a most inclusive one. Those who attend the complete series of meetings very obviously will hear presented certain final results of an effort in scientific investigation without precedent in the history of this or of any other country.

Contribution is a meaningful term. It implies that through the war our scientific medical knowledge has advanced to an extent beyond that which could have been expected in a peace time period of similar length. The truth of this implication is self-evident. Any single one of the outstanding developments which will be discussed at the meetings of this Fortnight would have been a most notable accomplishment for a whole decade of research done at the tempo of the 1930's. Each one furthermore is capable of direct practical application to the practice of medicine. These advances are most desirable things. They represent indeed notable not only for what each one has directly contributed

of disease, but also because of what each one means indirectly in terms of possible developments to be expected in the future

It is the duty of every physician to apply effectively in the care of his patients those scientific advances which have been proven to be of value. Every physician has an additional responsibility. This is to facilitate in every way in his power the making of further advances. This series of lectures should provide an ideal opportunity to consider not only the outstanding war time triumphs of the scientific method in medicine, but also to consider for future application the way in which these triumphs were brought about.

Let there be no mistake about it. Each one of these great discoveries which is presented here as an accomplished fact represents the end result of almost interminable labor, of unending disappointments and frustrations, of legions of false leads followed and of theories discarded. More than this, however, they represent something which sets apart the contributions of war medical research in contrast to the studies on similar subjects in peace time. This something is the organization and direction of research toward the solution of a specific problem or problems.

Organized work may be called development as opposed to research, if you choose. Whatever it is called, it has given in the past 4 years to medicine and to the public the advances which have been bitterly needed since the dawn of civilization. If these advances are desirable ones, and few would question the desirability, it is pertinent to review briefly here how their production was accelerated during the war. Once the means, or technique, is clearly in mind, we may consider how by the same or a similar technique a similar rate of progress can be continued during the peace.

Perhaps the first point to be established is whether we wish to continue medical advance at the rate now attained. Few individuals would oppose continued productivity unless they felt that the cost was too great in terms of fundamental human values, such as individual liberty, or possibly would interfere with long term advance. Interestingly enough many do maintain both these objections. This fact is well illustrated by the recent discussion which appeared in the columns of the *New York Times*. The basis for this discussion was a report by Dr. Vannevar Bush to the President of the United States, entitled "Science: The Endless Frontier." This report was prepared in com-

pliance with a request from the President for recommendations as to what can be done now in the war of science against disease to organize a program for continuing in the future the work which has been done in medicine and related sciences during the war. In the preparation of the report exceedingly careful consideration was given to the opinions of a very large group of individuals eminently qualified to discuss the matter. An important conclusion was reached. This is that if progress in medicine is to be maintained the government should extend financial support to basic medical research through grants both for research and fellowships. Another conclusion is presented which raises certain very important questions. This second premise is that "the striking advances in medicine during the war have been possible only because we had a large backlog of scientific data accumulated through basic research in many scientific fields in the years before the war."

A third conclusion is a corollary to the second and reads, "Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."

These 3 conclusions warrant serious thought. They imply, in essence, that the only way to maintain progress in medicine is to provide support for the accumulation of scientific data through basic research in many fields. This statement is made in the face of the evidence that organized research in certain limited fields during the war resulted in advances more rapid than would have been made without this organization and direction. In short, the advances which are to be presented at this Fortnight, as well as those made during the war in almost every field of science, cannot be continued, it is claimed by the very means which produced them during the war.

Only one conclusion, then, is possible from the public summary of the best scientific opinion of the country. We must concede that it is impossible to do basic research and at the same time to make striking advances. This is equivalent to saying that research and development are mutually antagonistic; hence since we cannot have both it is said let us provide Federal funds for the support of research and let development look after itself. The experience of the past suggests that under this system development lags and long periods often decide eclipse before the fundamental observation is converted through development into something applicable to the cure of the sick. Thirty years elapsed between the production of pancreatic diabetes and the

availability of insulin

The public and the practitioner are vitally interested in the maintenance of broad activity in fundamental research in all fields of science. They are equally vitally concerned to see that fundamental discoveries are developed to applicable techniques as quickly as possible.

Let us be sure, then, that the lessons of this war are remembered and converted into action. Let the physician and the public be vocal and demand that the present rate of medical advance be continued. If we cannot have concurrent research and development under the existing facilities, let the facilities be expanded. All power to the explorer, to the contributor of new, unexpected and basic facts through the increase in the general backlog of scientific knowledge. All power to the unsung hand of the developer, whose work, though equally laborious, is less spectacular. Let us be certain that we have the very best basic research possible and let us demand that at the same time development keep pace. If this require planning and initiation and organization, as was the case during the war, let us have these but in such a way as not to interfere with individual freedom and initiative. But withal, let us not lose sight of the fact that development has a place. Both the prospector and the miner are needed to get out the gold. It is the gold of the applicable discovery that is needed by the million occupants of our hospital beds and by the physicians who wish to help them.

## MODERN CONCEPTS OF WAR NEUROSES\*

*The Ludwig Kast Lecture*

BRIGADIER GENERAL WILLIAM C MENNINGER, MC, AUS

Director Neuropsychiatry Consultants Division Office of The Surgeon General U S Army

As a conservative estimate, there are at least a million more people in this country tonight than there were three years ago, who have heard of, have dealt with, or are personally concerned with that medical entity called psychoneurosis. Many millions more are familiar with pseudonyms for this illness—operational fatigue, combat fatigue, combat exhaustion. From the language of the G I, one could add more terms descriptive of neurotic reactions such as gang plank jitters, slap happy, bomb happy, reple deple exhaustion, etc. We in medicine are confronted with the fact that the membership of the military and their families at home have become increasingly educated on this subject, for better or worse, during the last three years. It is now a paramount responsibility of the medical profession, not only to correct much of the misinformation that exists, but far more important, to understand and effectively treat this illness. There are many former soldiers among the three hundred thousand odd veterans who have been discharged from the Army because of this illness who will need medical help.

There is a certain incongruity in the fact that it was the war which directed such a bright spotlight onto neurotic illness. Certainly no medical condition which occurs in civilian life can compare in incidence with the psychoneurotic problem, the origin of which lies in the conflicts caused by the pressure of everyday activity, the competitive nature of economic and social life. About fifty per cent of all who go to a physician present primarily emotional difficulties that correctly classified are some type of psychoneurotic reaction to the problems in their lives. With this civilian background, it is not surprising that the strenuous existence of the Army precipitates further neurotic expressions. Thus life in the Armed Forces focused conspicuous attention on this charac-

\*Lecture given before the Ludwig Kast Lecture Series, The New York Academy of Medicine.

teristic of the American people

Even more significant than the large number of individuals who are diagnosed by the doctor as psychoneurotic, is that sizeable segment of the populace which makes a difficult adjustment to life, though never develops a neurosis. They manage to get along reasonably well only because of some sort of support, some special indulgence, some particular type of relationship. There are many variations in such adjustments—the husband who lets his wife assume the masculine role, the wife who plays this role, the joiner and the hermit, the braggart and the gossip, the daredevil and the timid soul. They are the objects of our observation and comments in the closed circle of friends and family. They are not patients of any doctor and may be productive members of the community. They are, nevertheless, neurotic. We, those of us with any psychiatric insight, should not fail to appreciate that all the rest of us make use of neurotic defenses to some degree, always when under special stress of the environment and often when the stress is entirely internal.

With the psychoneuroses and the neurotic adjustment reactions, psychiatry is familiar. The growth in our knowledge of the understanding of the anatomy and the physiology of the personality has given us a reasonably clear picture of the mechanisms behind such relationships and behavior. It is the consensus of the great majority of the psychiatrists in the Army and the Navy, that the same mechanisms are operative in the military and that the same clinical pictures occur as we see in civilian life. Essentially, the response is the same when John Smith cannot adjust himself to the family at home or the artificially created family situation in the Army, when Paul Jones cannot stand the tempo of the factory and is unable to stand that of the Army.

There is, however, a group of reactions in the Army which does deserve special consideration because of certain features in the dynamics of its development that are characteristic. There are personality disorders occurring in the course of combat which, though not new, are at least different from those customarily seen in civilian psychiatric practice. It is this limited field to which I shall devote my attention.

#### BACKGROUND FOR UNDERSTANDING COMBAT EXHAUSTION

A prerequisite for understanding either pathological processes or pathological states is a knowledge of the normal. This entails not only

anatomy but physiology and applies to the psyche as well as to the soma. In spite of the difficulty of condensing such an explanation into the time allotted here, it seems desirable to set forth certain fundamental facts regarding the personality and its functioning that are well known to dynamically oriented psychiatrists, in view of the fact that the main point of this discussion is psychopathology.

A child is born, as any other quadruped, primitive, cannibalistic, asocial and uninhibited. The personality at birth is endowed with the two recognized fundamental drives of aggressiveness and erotism, perhaps more broadly described as destructive and constructive urges, as hostility and love. With growth and training the personality develops its individuality with a conscious regulating portion which becomes the ego. The child learns to curb his instinctive infantile behavior through the training and supervision of his parents. Initially all restraint is exercised by these external powers. The child learns to control his aggression and is rewarded with love. Beginning in his early childhood, he unconsciously incorporates this control function within himself and psychologically includes this function of his parents within his own personality as his conscience.

When the personality is mature, failure on the part of the ego to control the aggressive impulse is always accompanied by anxiety. Consequently anxiety comes to be a signal of disturbance within the personality. The impulse acts as a threat to the security of the ego which has from experience the foreknowledge of the disapproval from the conscience. The picture becomes complicated when there is in addition to the internal threat, an external threat in the form of danger. Psychiatrically, it may or may not be rather simple to differentiate anxiety which arises because of a disturbance within the personality from the apprehension or fear that arises from the external situation. Thus, the compulsive individual often may manifest anxiety without any external danger or threat. In some instances we see great apprehension or fear due entirely to external danger which superficially may resemble anxiety. Or they may be combined as in the case of the combat soldier.

Thus in a very over-simplified condensation of the dynamics of anxiety we see that its origin is the unconscious aggressive impulses which threaten the ego which if it fails to control them is criticized by the conscience. The conscience also becomes of special significance to the combat soldier in that its critical faculties of certain behavior are re-



laved and its individual idealism or code is, to some degree, displaced by the group code. Its development, and in fact the development of the total personality, is subject to many variations with numerous potent influential factors.

The relationships of the soldier with his father and with his siblings may both greatly influence his acceptance of his military role. Ideally the child likens himself to his father, following an initial and important struggle in his orientation toward authority. When this identification has been relatively smooth, the son accepts the role of submission to this father authority, becomes dependent upon him and borrows psychological strength from the process. Where the ideal role has varied and the son has developed no identification, where he has continued to resent the father and his authority, one must expect difficulty in all subsequent situations where the individual must be subservient to a father figure. This has frequently been encountered in the adjustment of the soldier to his leader and is of special significance for the man in combat. Except as eccentric daredevils, such soldiers are a liability in combat, but only a small minority fall in this category. The great majority transfer their original unconscious relationship toward the father to their commanding officer.

Further complications in the development of the personality are of special importance in some soldiers. Even in ideal maturity, recognized unconscious patterns of reaction exist between siblings. Associated with these are positive and negative feelings of affection and hostility. In the soldier's situation, the buddy may unconsciously come to represent a particular sibling and his reactions are, to some degree, predetermined by his relations to his true sibling. Sometimes there is a strong attachment with minimal negative feelings and sometimes a strong attachment despite strong negative feelings. Army life in itself is often conducive to very strong attachments between men. They share training, experiences and dangers. When one is wounded or killed, such experiences alone may explain much of the reaction. On the other hand, where a previous sibling relationship existed in which there was unconscious hostility, this may be the chief determining factor in the symptomatology of a breakdown. One must postulate that in all cases, the early family relationships condition the soldier's behavior toward his associates.

One must not ignore other factors operative during the formative period which have also influenced the pattern of the soldier's person-

ality These make up the total social environment in which he grew up to function as an individual Civilization represents an extension of the original parental influence as a curb of the primitive man which aims toward social maturity of his group For the soldiers in this war there were many special national problems and attitudes present which directly influenced their childhood and adolescence Some of these were parental unemployment, the struggle of democracy versus dictatorship, an isolationism in attitudes of our people toward the rest of the world There were the good and the bad effects of radio, screen and transportation speed which developed concurrently with the soldiers of this war

In addition, the tradition of the American culture is to produce a personality with emphasis on individualism and independence Deeply ingrained self-respect and a high degree of self-determinism were American characteristics and these were coupled with a free and unrestricted privilege of self-expression Such were the influences to which the personalities of our soldiers were subject

#### NEW ENVIRONMENTAL STRESSES IN BECOMING A SOLDIER

Pearl Harbor caught us unprepared to aggressively express ourselves in war against another nation In contrast to the belabored debate of the months preceding, as to whether or not the show in Europe was any affair of ours, the psychological effect of Pearl Harbor on the nation was to cement us into a singularly unified attitude Unfortunately before many months had passed that unanimity of opinion and determination of purpose became somewhat decimated and vague At the same time, men were regularly and speedily taken into the Army in large numbers What was their motivation as they joined the Army? One has to conclude that in a great majority of instances these men being law-abiding citizens came in because it was the will of the country Not a few had a resigned attitude and undoubtedly the lack of emotional tone in the populace at large led many to feel that fate had played them a poor game They went because it was their duty but rarely with enthusiasm or conviction

When the man became a soldier there were changes in his external situation which demanded major readjustment He gave up his normal gratifications almost entirely He had to accept separation from his family his home his job his friends with little in prospect except the possibility of adventure He had to give up his individual identity and

become a member on a team, with the only reward being his identification with that team. He had to accept severe privations in return for very restricted gratification.

For that group of men who had to go into combat, there was another series of adjustments required, those for which there is no parallel in kind or degree in civilian life. The personal danger surrounding the combat soldier made all other adjustments pale into relative insignificance. The necessity of throwing over all previous ideals, not only of his own conscience but of the group conscience to accept the requisite of killing to avoid being killed was a greater change than many people realize. Frustration was a daily part of his life, sometimes in the form of waiting—days, weeks, months, sometimes in the deprivation of essential supplies. Confusion was routine in his life and the noise and whistles and flares of battle are beyond the imagination of anyone who has not heard and seen them. Insecurity was constant, not only in his personal doubts of himself, but also the doubts regarding his orders, doubts about the leader's ability, and knowledge, doubts as to whether the higher-ups understood and would act, or permit him to act. In addition to all this, was the extreme physical discomfort, the loss of companions, the ever present pain and death.

All of these factors operated on the personality and it is amazing that so many American men tolerated them so effectively. There were comparatively few compensations, few supports against all these pressures. But without question it was these supports that enabled them to function. Probably the most important of them was the leadership of the unit. Psychologically the leader is well recognized as representing the strong father figure who is interested in the individual, who is looking out for him, who is considering him, who knows what he can do and actually leads him. Nearly as important as the leadership, however, was the group identification, the esprit de corps created by close association, the common aim and mutual sacrifice. Many soldiers freely admitted that it was chiefly because of their feelings of loyalty and devotion to their associates that enabled them to go on. Their individual civilian-life conscience was displaced by a group conscience, which served both in a positive and negative fashion. Positively it gave them permission to kill—a behavior antithetical to their entire life ethics and training. Only through group permission and approval could they do it and even then it was often very difficult. The group conscience sup-

ported them in a negative way—it prevented them from quitting because of the fear of group disapproval. The close personal attachment to and dependence of a soldier on one or more members of his group, his buddies, was a very important force in maintaining his combat ability.

Other definite aids to the withstanding of the external stresses of combat were the soldier's training in discipline and obedience and along with it the confidence in his own ability and in his weapons which was developed through such training. He was sustained by his own physiological responses, the result of stimulation by excitement of the autonomic nervous system which enabled him to be aggressive. A minor, but in some instances an important reinforcement was the glorification of the mission in which he was partaking, a glorification which in the extreme made even death seem a little less unattractive, at least he faced the prospect of a hero's death.

#### PSYCHOLOGICAL CHANGES IN A SOLDIER TO MEET THESE EXTERNAL CHANGES

While one may enumerate the various supports and compensations which helped make a soldier able to face combat, they alone were not enough. Less apparent dynamic changes in the personality were necessary to effect adjustment. It is important to recognize that in the majority of instances these changes are unconscious and therefore automatic, but without a doubt must occur for the individual to effectively meet the demands made upon him. The first of these is to change from his civilian independence with initiative and self-expression to a dependent role of submission to leadership orders and group requirements. Granted that the soldier has an opportunity in a limited degree to develop his individuality in certain isolated instances, the winning of a battle demands that the good soldier rely on his superior and that he accept and carry out his superior's orders promptly and exactly. He must therefore accept a predominantly dependent emotional role. This acceptance, while difficult for some, is welcomed by others. In any event this change may bring unconscious satisfaction in that it requires the man to shed responsibility—to live on the decisions of others—to have his daily life planned—to passively be the recipient of his food, his clothing, his shelter, such as it is.

This passive relationship grows more rapidly and becomes acceptable when the soldier feels secure through his confidence in the symbolically

all-knowing, all-powerful father, his commanding officer. Subservient to this officer and under his direction he learns to modify a lifelong constructive drive in order to allow the functioning of a primitive, destructive one. Only with this help can the average man shift from a constructive civilian life to a chiefly destructive soldier life. Even so, the change is so difficult that severe psychological problems arise.

Many soldiers never had to make the psychological adjustment to the process of actual killing and seeing the result of their aggression. The bombardiers, the artillerymen rarely, if ever, saw the result of their work at close hand. In contrast, the infantry soldier often, if not regularly, was in a position to observe his effectiveness. Because of this there were many instances when soldiers who could not bring themselves to kill, even under the pressure of facing leader and group censorship, became ill from the psychological conflict involved. In other instances, a soldier might reach a saturation point, a limit to his ability "to take it"—referring specifically to his necessity to kill.

Other factors come in play in those occasional situations where hand to hand combat takes place. There the imminent external threat is sufficient to overcome the influences of the conscience, even in those who under less threatening circumstances found difficulty in killing.

Another dynamic change in the functioning of the soldier's personality is the necessity to shift his investment of affection from individuals to a group. Throughout his life he has had a fixed and more or less constant association with certain individuals—mother, father, siblings, wife, children, long-time friends, with whom he has shared love and interest. They have been, quite literally, his world. These he must temporarily set aside and from them he must shift, for his immediate investment of affection and return of interest, to a strange heterogeneous group of men, to a diffuse group love in contrast to his previously specific individual love. Certain members of the unit gradually become his inner circle, and maybe his chief support, but the major identification for an effective unit must be made with the group and he must fuse himself with it.

This review of the dynamic forces in the life of the soldier about to go into conflict indicates that he must accept an emotional regression to an earlier developmental stage in order to permit his acceptance of the essential dependent passive role. This does not imply that he must make an intellectual regression or that the whole procedure is accom-

pished with considerable insight. It is nonetheless through such regressions that he can mobilize and express the primitive aggressive drive present in everyone of us which is essential to the functioning of a fighting man. This regression in no sense lessens his need to protect himself and undoubtedly the external threat is a major stimulus to the expression of this aggressive drive. It is through the full approval of the good (father) leader that the dictates of the individual and personal conscience can be ignored. If either the leader or the group approval is not constant, the soldier's main psychological support is lost. Consequently we must recognize that the soldier, even before he starts combat, is in the predicament that not only is he faced with an extremely dangerous external threat but with a potential internal threat.

#### THE DEVELOPMENT OF A NEUROPSYCHIATRIC REACTION IN COMBAT

One must see the combat casualties in this stage setting. In general, there are two large groups of reactions with no sharp dividing line: first, those individuals who are grossly predisposed to maladjustment and second, those with minor or no apparent predisposition. In the first group, the combat casualty presents a familiar neurotic response, similar to the picture seen in civilian life. Even though the soldier had succeeded in making a possible adjustment to all his pre-combat training, the stress, and usually some specific feature of combat—upset the balance of his equilibrium. Such patients initially present typically neurotic defenses—conversions, obsessions, psychosomatic complaints, etc.

In both of these groups one may observe various devices used to protect the individual against his anxiety. Many soldiers adopted a fatalistic attitude expressed in the remark, "one of them has my number on it and when it comes it comes." The utilization of omens, charms was common. These all represented a magic protection of the ego and were common to all soldiers. One could discern cumulative effects of various events although the anxiety is controlled. With increasing fatigue one might often note a slight impairment of the individual's judgment, his tendency to carry out repetitive activity, such as jumping in a fox hole without adequate testing of the reality situation. Such automatic responses were even active in places of relative safety. In many instances a narrow escape, the death of a platoon member were contributory. A very common observation was the case of a wounded man who only began to develop anxiety as his wound healed and he

was confronted with a return to combat duty

A second group of soldiers, certainly the majority, appear, at least superficially to be normal personalities reacting to abnormal stress. They give no history of previous maladjustment in civilian life, no history of distress to themselves or their family. However, these soldiers must have some predisposition, minor though it may be. Undoubtedly, the outcome of their reaction to combat depends on the degree of this predisposition. It is gratifying to know that the majority, probably the great majority, responded sufficiently under appropriate treatment to permit them to carry on. That their experience leaves scars, there is no doubt, but certainly in many, these scars are not sufficient to seriously or permanently disable them. Our figures indicated that sixty per cent of the psychiatric casualties from combat were able to return again to service in the Army area, and at least fifty per cent of these, in certain instances more, returned to actual fighting. We should have no illusions, however, about this group. The Army medical officer's function was to return the soldier to duty. Neuropsychiatric casualties, if adequately rehabilitated, were no less expendable than rehabilitated surgical casualties. If they were well enough to do further duty, that was their assignment, and many carried on indefinitely. The permanent effect of the Army experience, and specifically that of combat, on their personalities will only be known with the passage of time.

There is also a group of men, in whom the predisposition, even though not apparent on the surface, was serious enough so that they did not respond quickly to treatment. An additional larger number showed a delayed reaction, they completed their tour of duty and only then, under different circumstances, perhaps as they returned home, did their psychological battle scars manifest themselves. In every instance of these delayed reactions, there is very good evidence to believe that there was a specificity for the individual in the final event or situation which served as the precipitating factor.

Grinker and his co-workers very adequately describe the various types of regressive pictures based on their chief symptomatic expressions under the groups of passive dependency, psychosomatic reactions, guilt and depressive reactions, aggressive and hostile reactions and psychotic-like states.

The immediate clinical picture was colored far more by the combat situation than by the individual's particular personality. This was as

true of the man who broke down in the first few days as of the man who broke after many months of combat. Their clinical pictures were remarkably similar. From a psychological point of view, such reactions were the result of cumulative stress. In both cases the man had reached his limit as a result of physical fatigue, the continuous threat to life the single or repeated psychological traumata all of which had exceeded his capacity to handle.

The clinical picture has been described by several combat experienced psychiatrists. The prodromal symptoms are most frequently irritability and disturbance of sleep. The individual is aware of his increased sensitivity, his "startle reaction," his involuntary self-protective motor responses to sudden noises. Sleep becomes disturbed because of sudden involuntary starting or leaping up because of noise stimuli or disturbing dreams. The soldier himself may recognize his symptoms or the man's behavior or change in personality becomes apparent to those about him. He may become more seclusive and silent, or on the contrary more talkative, he may be restless, may smoke excessively if the opportunity permits. He is aware of an increased apprehensiveness but paradoxically is less able to concentrate. He frequently shows somatic symptoms such as mild tremor, incontinence of urine or feces.

There was a monotony in both the complaints and the symptoms as seen by the physician in the aid station or by the psychiatrist at the clearing station. The complaints differed depending upon the stage of personality disorganization, in the majority of cases they followed a stereotyped pattern. "I just can't take it any more." "I can't stand those shells." "I just couldn't control myself." The symptoms varied only slightly from patient to patient. Whether it was the soldier who had experienced his baptism of fire or the older veteran who had just lost his comrades, the superficial result was very similar. Typically he appeared as a dejected dirty weary man. His facial expression was one of depression sometimes tearful. Frequently his hands were trembling or jerking. Occasionally a man would display varying degrees of confusion perhaps to the extent of being mute or staring into space. Very occasionally he might present classically hysterical symptoms. Some of them knew that they were "combat saturated" and that they might be through so far as fighting was concerned.

Such is the common immediate reaction one that does not on its early symptomatology fit into any of our known diagnostic categories.



For this reason, the widely used terms of combat exhaustion and operational fatigue have probably been very practical for their utilitarian aspect. They have the disadvantage of implying that physical exhaustion or fatigue plays a major role. It no doubt does contribute an influence, varying in different situations, but it was never possible to set up a series of physiologic experiments which might have given some index as to its actual effect. On the basis of broad experience, it has been estimated that not more than 3 to 5 per cent of the reactions were due entirely to fatigue. In the other 95 to 97 per cent the condition was primarily a personality disturbance and was treated as such.

The commission of five civilian psychiatrists who visited the European Theater in April and May of this year were united in their opinion that the picture of psychologic disorganization did not correspond either in its moderate or in its extreme form to any recognized or established psychiatric syndrome. They regarded the term "combat exhaustion" as a practical term to apply to this temporary condition, out of which various more definite and more familiar syndromes evolve. This diagnostic label does not apply beyond the initial state, and as such represents a transient psychiatric reaction to combat, that may or may not progress to a more clearly defined clinical entity. Consequently, it has no applicability beyond the immediate response. It does not apply to the further evolutionary stages, the typical psychoneuroses, nor does it apply to the delayed symptoms so often seen, those typically regressive phenomena, in men who have completed their tour of duty, which occur at a time when the support of the group and the leader is gone.

#### PSYCHODYNAMICS OF COMBAT EXHAUSTION

The psychodynamics of combat exhaustion include four significant features: the depleted ego strength, the specific precipitating trauma, the mobilized aggression and the loss of the ego supports in the form of leadership and group identification. The depleted ego strength, the ability of the conscious personality is in every case cumulative, regardless of the length of combat. One must assume that certain types of personalities can withstand stress over a longer period of time than others, but the breakdown of the soldier in combat, whether it is during his first week or his fifteenth month, is related to his ability to withstand the stress, plus the avoidance of any specific psychological trauma which would overbalance his ability to adjust to the external demands. How-

ever, the cumulative effect is a major factor, so that whenever the specific traumatic event does occur, it may in some cases appear trivial. Just as in civilian psychiatry, though it is often not possible to discern the specific precipitating factor in the production of mental illness, there is much evidence to believe that it is always present. The soldier may or may not be able to describe certain events which may have been the final straw—the death of a comrade, the hopelessness of a particular assignment, a broken promise.

Two factors permitted the soldier to express his aggression. One of these was the external situation, the necessity either to kill or be killed. The other and probably the more significant, in the situations which were less immediately threatening, was the approval and command of the leader and the identity with the group which shared the common aim. When and if these psychological factors suddenly disappeared, one found the dependent ego with a high degree of activated aggression with no outlet to express it. In the very rare situation, the soldier might carry on alone, such were likely to be the winners of Congressional Medals of Honor. Much more often, with the loss of the leader and/or the group, the soldier was at a loss. The combination of his helplessness and his activated aggression invariably created anxiety.

It is the ego's normal function to maintain the integrity and equilibrium of the personality against both the external stress and the unconscious forces within the personality. It is helpful to think of the ego as having a given strength, of a strong or weak ego, of increased or decreased ego strength. In the combat soldier, the continuing effect of combat accumulates and drains the ego's ability to maintain balance. In the specific traumatic event of the final wound, it must attempt to control a powerful aggressive impulse which it can now do with only limited success. Its failure gives rise to anxiety which, if transformed into symptoms, comprises the clinical picture—the irritability, the sensitiveness and jumpiness, the depression, the inability to concentrate or accomplish even relatively simple tasks, the dreams which recur so characteristically in the combat psychoneurotic personality.

In many medical conditions, even the pathology represents an unhealthy attempt to rectify or alleviate the cause of that pathology. This phenomenon is even more pronounced in psychiatry in which the symptoms are, in a sense, an attempt at a solution of a conflict. A special characteristic of some mental symptoms is the tendency to repetition,

so brilliantly described by Freud as a repetition compulsion. This process is a conspicuous feature of combat exhaustion and is perhaps best illustrated by frequent similar dreams. The dynamic significance of the dreams, in general, is that they are an effort of the unconscious to resolve the conflict by mobilizing the anxiety to expression. Because the whole dream process is unconscious, the individual is not relieved and may be so disturbed by the dreams that the illness is aggravated. This creates a situation in which the individual is stimulated but is not permitted physical expression, and the more the physical expression is inhibited, the greater becomes the anxiety. Unless there is aid given to bring the conflict and its resolution to the conscious level and into reality, the neurosis continues. What was originally stimulated by an external threat becomes internalized and without help may become an insoluble vicious circle. The unconscious emotional pressure continues to produce anxiety in increasing amounts without conscious recognition of its causes.

### CONCLUSIONS ABOUT THE WAR NEUROSIS

In summarizing the main features of the war neurosis discussed above, one needs to remind himself that this group of reactions to combat represents only a small percentage of the total psychiatric problem of the Army. It does not include the neurotic reactions occurring in basic training, on boarding ship, in sitting on a lonely south sea island, in weathering a monsoon season in India. Nor does it include the 25 per cent of all types of discharges for psychiatric reasons because of warped character development. All of these groups are familiar to psychiatry and differ in no way from the same pictures in civilians except in the environmental situation in which they developed or became apparent. Very often they were revealed only because of that situation, they might have gone unnoticed in civil life.

Only combat reactions, represent the true war neuroses. They too become apparent only because of the situation. They have been described as the normal response to abnormal situations in which the stress was far more severe than in civilian life. It is reasonable to assume that many men developed these reactions who might well have gone through civilian life without manifesting any gross maladjustment. Furthermore, many who did suffer from such traumatic experience apparently recovered quickly, even to the extent of successfully continuing

the same severe test of adjustment

In summarizing the dynamics of combat breakdowns, there would appear to be a combination of the severe cumulative external stress, a varying degree of predisposition, a peculiar psychological setting in which the combat soldier functions and a specificity of some particular event which precipitates the incapacitating result. Any or all of these may vary in each individual case, some of them being all important in one instance and inconspicuous in another. When the final straw is placed on the soldier's back, the immediate result appears very similar in all cases. Fortunately, with relatively little help the majority promptly readjust. For the remainder, and numerically the group is large, there was and will be need for further psychiatric treatment.

Only as we understand these dynamics can we understand the symptoms which we may see in the veteran patient. His weakened ego cannot handle the aggressive forces which have been activated. His solution is to regress to simpler functioning level. In some cases, instead of returning to his normal adjustment he remains in the regressed stage of development where he can express his passive dependency, his depression, his hostile reactions, his somatic complaints. He cannot explain his symptoms—his feeling of helplessness, his stomach disorder, his irritability and impatience, his tendency to fly off the handle, his failure to find satisfaction, his resentfulness of all but his own group. Some will return to civilian life with a tendency to feel that no one understands and with latent, or expressed, paranoid attitudes. They do return, in a sense, to a foreign atmosphere but their attitudes are not caused so much by this fact as by their personalities which are heavily burdened with the conflicts arising from their battle experience.

With this understanding on the part of the physician, treatment must be directed toward integrating the individual into his pre-war identifications and satisfactions. If he comes with emotional problems, with pent-up resentment which he cannot manage, these must obviously be released. With this release must come insight through psychotherapy, not only into the immediate situation but into the origin of these emotions in their relation to previously formed personality patterns. What is the treatment and by whom should it be given? No simple set of rules can be laid down but some patients are going to require expert psychiatric care and others can certainly be helped and probably readjusted by the intelligent, sympathetic physician who has some psychi-

attric orientation. In other words, some patients, to borrow an analogy from surgery, will need major and others minor psychiatric procedures. The former should be carried on by an experienced psychiatrist, the latter could be adequately directed by a general practitioner or a specialist in another field.

One might generalize by saying that if the patient has made an attempt to fit into his civilian situation and is consciously aware of his symptoms, is preoccupied with his traumatic experiences in the Army, has recurring disturbing dreams, the chances are that he should see a psychiatrist. Just what the treatment would be is hardly within the province of this presentation. In the Army, we have found that psychotherapy under sedation is a valuable short-cut to relieve the pent-up emotion. Hypnosis has also proven to be an effective therapeutic tool for this purpose. In both of these types of treatment, the ultimate success depends upon the skill and the knowledge of the psychotherapist.

On the other hand, if the patient is exhibiting minor evidences of anxiety in the form of restlessness, minor physical complaints or problems of adjustment to the people around him, it is very likely that the general practitioner can and should help meet these problems. In so doing, he needs to appreciate that sometimes he can help directly by merely being a good listener and pointing out the inconsistencies, the discrepancies in the man's thinking and feeling processes. Very often he can make positive suggestions with regard to the manipulation of the environment. If one could insure sufficient family affection, economic and social security, easily accessible ego gratifications and good physical health, many of these veterans would be helped if not entirely rehabilitated.

When one takes into consideration the fact that 315,000 soldiers have been discharged from the Army for neuropsychiatric reasons, he may grasp the importance of this problem as a post-war challenge to medicine. A fair percentage of these have had combat experience and will present the dynamics and the clinical picture described in this presentation. It is to be hoped that all physicians will prepare themselves to accept and to treat what the Army medical officers discovered were among their biggest problems—the emotional factors in the production of illness.

# WHAT CAN THE PRACTITIONER DO IN TREATING THE NEUROSES? \*

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THIS brief presentation cannot hope to teach the techniques of psychiatric therapy. But if it should serve to stimulate interest, sympathy and cooperation for better medical care of sick people, it will have done much. The practitioner's function is to treat people, not diseases. There are few diseases that have not their emotional components, and this is often of first importance in the etiology, the course the disease may take, the length of convalescence and recovery or chronicity. The old-time family doctor was uniquely successful in treating his patients because with no knowledge of psychiatry he knew them as people, their families, their backgrounds, their communities, and their day-by-day problems. With the increasing specialization of medicine, and the growing preoccupation with particular areas of the human body, the person having the disease came more and more to be neglected. The specialty of psychiatry has brought into modern medicine a renewed emphasis on the importance of knowing a human being and it has developed specific techniques and procedures of scientific validity for the understanding of the person. With knowledge of these principles the physician will be in a better position to practice what Dr. David Barr felicitously calls "comprehensive medicine." Could such an orientation be guaranteed to every young graduate there would be less unnecessary surgery performed, more patients would be provided support and understanding throughout their illness and numbers of human beings could be spared the process of running fruitlessly from one doctor to another in search of help which they do not find. The practitioner is in the major position to help troubled and emotionally sick human beings. To

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\*\* In the organization of this paper full credit is given to Gen. Wm. C. Menninger and to his publication of War Dept. Technical Bull. T B Med 94 which contains the most concise and helpful statement for general medical men the author knows.

this end it is of the first importance to attempt to elicit from every doctor his interest, sympathy, curiosity and his desire to help sick people in the fullest sense

War and the experience of army doctors has brought a renewed awareness of this need and has revealed disturbing facts concerning the number of people who require such attention. Wartime findings have revealed that over two million able-bodied men are in need of this kind of medical help: 1½ million psychiatric rejectees revealed by selective service, ½ million discharges for psychiatric disability and ¼ million suffering from psychosomatic or neurotic components in their disease process. There is little fundamental difference between the neurotic responses of veterans and those of ordinary civilian experience. Behind all these war neuroses lies the same etiology. In the military experience the precipitating stresses are greater and the dynamics are more readily available and more easily understood. The principles of treatment are the same. These facts of prevalence should not have been surprising for we have always known that 40-60 per cent of all patients who go to doctors need this kind of understanding for their cure. This same high incidence of emotional disturbances is evident in patients admitted to general hospitals for conditions not recognized as emotional in origin: 27 out of 100 at the University of Chicago Hospital, 30 per cent at the New York Hospital. This presentation tonight might not be necessary if there were enough psychiatrists to begin to meet the problem. Only about 3500 exist out of a total of 185,000 doctors. It is evident, therefore, that if the vast majority of these and other human beings are to be helped, it will be by the general practitioner.

In analyzing the failures of our past medical efforts certain difficulties can be offered in extenuation. The psychiatrist has failed in his task of education. He has been too long isolated from the stream of general medicine. He has worked in hospitals remote from general hospitals, he has been unable to share his specific knowledge and techniques, too often beclouding his work in strange incomprehensible language. He is frequently a poor practitioner, unable to combine the resources of internal medicine and psychiatry in his diagnostic evaluations. On the other hand, the practitioner has remained equally aloof from psychiatry. He frequently has ingrained attitudes of pessimism and nihilism towards it. He lacks the confidence to attempt the evaluation and treatment of emotional factors. He complains of the time involved in the process and

claims that the techniques are intangible and non-scientific. Such objections are not valid. To be sure time is involved, but little more than in any really comprehensive physical work-up with its long delays in X-ray and laboratory studies. The results of psychiatric therapy are often striking and constructive as is seen in the rapid recoveries now obtainable by electric shock, insulin, hypnosis and the use of sedation-interview techniques. Psychiatric techniques are scientifically valid and although not measurable by the usual sensory perception methods of internal medicine, they are nonetheless grounded on sound principles of observation, evaluation, and the pragmatic test of recovery.

Until the practitioner's attitude toward psychotherapy can be brought to one of constructive optimism, little can be expected from him as a therapist. He must begin with the conviction that medicine deals not primarily with disease entities or organ pathology but with human beings reacting to various kinds of noxious stimuli. These may be chemical, bacteriological, physical trauma or emotional unrest. Whatever the precipitating factor the end result is the same—a sick human being. There is no such thing as differentiating between organic or functional, it is always both. Pre-eminently the practitioner still has to learn to recognize emotions in their many varieties and their effect upon the living being. His greatest effectiveness lies in the taking of a complete and proper history which gives due emphasis to the individual's emotional make-up and responses. He must learn how to establish an effective rapport or working relationship with his patient and he will succeed in this in direct proportion to the degree of genuine interest he shows. This is facilitated by his sensitive and kindly inquiry into the patient's personal life, his respect for the facts he obtains thereby, his genuine unfeigned desire to be helpful, his unspoken interest evidenced by his undivided attention, by his capacity for silence, by his facial expression—his smile, his gesture, and by his mere willingness to take the time to listen. He must learn to recognize that everything the patient says and does is of importance, that the patient's reactions during the physical examination may be as important as the patient's utterances in revealing sensitiveness and prevailing attitudes and emotions. Equally important, he must learn to observe and evaluate his own reactions toward the patient. Only thereby can he avoid those common pitfalls—that he will tell the patient there is nothing wrong with him, or that his troubles are "imaginary." Or he may immediately resort to sedatives for relief.



when they are clearly not indicated. He may put too much attention on the physical examination thereby heightening the patient's anxiety and implanting the wrong impression that things are seriously at variance from the normal. He may waste time in protracting his laboratory studies to no avail, or more importantly, he may let his own emotional responses color his evaluation and management. Unless he understands his own emotional life, he may err in the direction of too much sympathy, paternalism, and protectiveness, or the converse—indifference to the problem, abrupt dismissal of the patient, peremptoriness, show of annoyance, disdain, anger, scolding, or thinly disguised punitive behavior. Perhaps such self-analysis is asking too much of the practitioner. He may be little inclined to study or analyze his own emotional responses toward his patient. Although he would be a better psychotherapist if he did, it may be enough to ask that he learn to control his own emotional reactions to his patient. If his attitude is primarily disdain and annoyance toward neurotic patients, he should not try to treat them.

He need not be seriously concerned about psychiatric diagnostic terms. Diagnoses are at best convenient labels. They add little to the patient's understanding of himself. They often confuse and cloud the issue and they are quite unimportant compared to the understanding of the facts and how they work. The diagnosis of psychoneurosis can badly frighten a patient who is little prepared to understand its meaning and who has heard so much about it in these years of war, with all the unfortunate and frightening connotations that it so frequently and falsely conveys to the uninformed person. To tell him that he has a nervous illness or that he is emotionally sick is usually acceptable and does no harm to the facts or to the patient.

To every physician of experience certain common and frequent problems of an emotional nature present themselves daily in his practice. Common sense has taught him to recognize the psychotic or grossly mentally disturbed individual. He knows that delirious reactions can occur from fever, over-medication, alcohol. He has seen patients in postoperative states of excitement. He can easily recognize the seriously depressed individual with his suicidal preoccupations. With these problems he is relatively little concerned since they are obvious and usually require the psychiatrist's attention. More commonly, however, he will encounter the patient with well-defined organic illness who reacts with strong emotion to it resulting in delayed convalescence, protracted

symptoms and failure to respond to the usual medical regime Secondly he will encounter those individuals whose disease picture represents a combination of physical and emotional problems (such conditions as peptic ulcer, colitis, hypertension, asthma, etc ) where he needs to know that the patient's emotional state may be the fundamental cause, may aggravate, may explain fluctuations, or may indeed determine the entire course of the disorder This group of patients fall under the heading of that much misused term "psychosomatic illness"—that area of medicine in which the patient's illness is most effectively treated by the joint cooperation of internist and psychiatrist There is growing evidence to believe that many of these states begin first with emotional unrest and that protracted states of emotional upsets may ultimately lead to permanent and irreversible organic changes Thirdly he will recognize that group of patients whose genuine physical complaints are primarily expressive of emotional disorders These are the fatigue states and the insistent bodily or somatic complaints which the ordinary techniques of medical examination are inadequate to explain Fourthly, there will be those patients whose complaints are predominantly psychological in nature These individuals put to the foreground their symptomatology of anxiety, fear, obsessive thoughts and compulsive actions Some of all of these groups of patients may have spontaneously recognized the role of their emotional disturbances in the cause or particularly in the fluctuation of their symptoms They will have partial insight The practitioner may be as yet little acquainted with the fifth group of patients, those who present the interesting phenomenon of repeated accidents whom we have come to recognize as representing a special kind of personality make-up The industrial physician recognizes this group, for he knows that the majority of accidents occur repeatedly among a small group of workers The surgeon, the gynecologist, the genito-urinary and other specialists will recognize their particular problems of individuals who do not respond to repeated manipulations, who get persistently worse because of them, who may be rendered chronically disabled unless techniques other than physical manipulation are employed There are patients who seek and crave operations, others who seem almost addicted to genital, pelvic and cystoscopic procedures Finally, every physician must learn to recognize the depressed patient with his characteristic sadness, insomnia, weight loss, gloomy outlook on life, and his potential risk of suicide The practitioner can learn to treat depressions, anxiety

states, fatigue reactions, hypochondriacal illnesses, and psychosomatic disorders. He is not equipped to treat more involved neurotic reactions.

What, other than recognition, can the practitioner do about these disorders? First he must become convinced that these states are never conscious or feigned or deliberate, that they are beyond the average patient's capacity to resolve, that the true causes are largely unconscious or unknown to the patient and that they are always indicative of emotional conflict within the person. The simplest analogy is that which happens with anxiety. We are all familiar with normal anxiety responses, because we have all experienced it: the dry throat, the trembling hands, the tightening of the chest, the nausea, the diarrhea, the polyuria. The entire organism is involved in anxiety responses, and we have learned to study the cardiovascular changes, the increased leukocyte count, the metabolic and chemical imbalance accompanying anxiety. States of anxiety instead of being transient may become protracted, chronic, sweepingly disabling, and may arise whenever external stress or threat is present or whenever the threat derives from unrecognized conflicts within. Anxiety can be considered to be a natural defense mechanism of the human being which is called into play whenever the person is threatened. Many of the phenomena of psychiatry can be understood as the person's attempt to handle this anxiety. The patient may experience it directly with all its attendant physical discomforts. He may attempt to protect himself from its pain by the development of physical complaints. He may deny it and escape from it in the substitution of hysterical symptoms with its characteristic emotional indifference to the symptom. He may project it upon others as blaming and suspicion, or he may rationalize it to himself by all kinds of thinly disguised and false explanations. None of these mechanisms are deliberate, anxiety in essence then represents the attempt of the sick individual to achieve some kind of balance within himself. The degree of anxiety he can tolerate or the point at which any human being reaches his dilemma of sickness depends in part upon his constitutional stability and capacity to bear stress, by the severity of the noxious stimuli or events of his life, or by the degree and stress of his internal conflicts. It is important for the practitioner to recognize also that the organism can be similarly thrown off balance by other emotions such as anger, rage, resentment, fear, jealousy, and suspicion. The practitioner will be little effective, therefore, until he learns to recognize and deal with the vast range of emo-

tional responses of which people are capable

The mere recognition of these facts, although helpful, is not enough. What can the practitioner do about them once he is aware of them? In the treatment of these conditions he needs to know that hospitalization is rarely an adequate solution, that it may make the condition worse by providing too much attention, by putting a premium upon illness as a mode of reaction, by recourse to bed rest with its attendant increased preoccupations. These patients are best treated as ambulatory patients in repeated visits to the physician's office. Such visits can be brief, a half hour may suffice if the patient is not merely permitted to repeat symptoms but is obligated to search into causes. Similarly the practitioner should know that like most surgery the effects are best when therapy is begun promptly, skillfully and as early in the illness as possible. His main tool will be language and conversation. He must recognize that he will play a vital and significant role in which he will find the patient thrusts upon him all kinds of emotional feelings, few of which are related directly to him, most of which represent the transfer to him of feelings, attitudes, and emotional responses that have their origin long before in the patient's life. He must expect more than the positive emotions of respect and admiration. He must be equally prepared to accept the negative and hostile feelings which the patient may feel towards him. He must not be thrown off the track by the patient's anger, resentment, criticism or dislike. Some such feelings may inevitably appear as a phase in treatment. His therapy begins with his very first contact with the patient, is maintained throughout the physical procedures and hinges pre-eminently upon the process of history-taking. He begins with the patient's complaint, more often than not offered on a somatic level. He should not take the first utterance of the patient as the chief complaint for this often merely disguises the patient's fundamental problem. His next task is to understand the origin and development of the complaint in its chronology and in relation to the full activities of his patient's contemporary life, with particular seeking for evidences of dissatisfaction, conflict or anxiety relating to contemporary financial, occupational, marital, familial, social, religious, and sexual tangles. Very soon he will see that the onset of the symptoms frequently coincides with periods of particular emotional stress or disturbing contemporary events in the patient's life. This is the present illness, the step-by-step account of the appearance and development of the main

complaint in its total personality setting

With brief experience it will soon become evident that contemporary difficulties have their inevitable precursors in the earlier life period of the individual, that indeed they are commonly only repetitions of earlier and more basic patterns of adjustment or maladjustment. Where the material spontaneously emerges, a rigid history review may not be necessary. For the physician's own assurance of completeness of the review, and sometimes for the orderly accumulation of material, it is well to pursue a planned review. This constitutes the personal history. The patient is told that for the physician's fullest understanding of the current difficulties, certain early biographic material must be elicited. One begins then with the record of the patient's birth and untoward events: the outstanding data of the infancy and childhood period, the evidences of early instability in the form of nightmares, sleepwalking, enuresis and other so-called neuropathic traits. The outstanding facts are then elicited of the school record, performance, and extent of education, the work record in terms of actual job successes, failures and reasons for change, the family status as to actual members and relations thereto, the place of the patient in the sibling group. The marital history and status is obtained chronologically with particular emphasis on the adjustment to husband or wife, the relations or worries about children, the general satisfactoriness or unsatisfactoriness of the sexual adjustment. It is well not to force confessions about sexual orientation during the first interview but to await the development of full confidence before eliciting the details of what is the most sensitive area of most patient's functioning. The general religious, racial and social adaptation as it relates to friends and community is surveyed for particular evidence of difficulties or failure of adjustment. The history of degree and extent of use of tobacco, alcohol, medication and drugs must be obtained.

A brief review of the family history is necessary with particular attention to the incidence of similar complaints among family members and to the incidence of more sweeping nervous, emotional or psychotic difficulties. The personality description spontaneously given by the patient as to his outstanding traits of personality make-up gives interesting leads as to undue emotional lability, dependency, conscientiousness, meticulousness, anticipatory anxieties, resentments, and hostility feelings.

The completion of the review will give the physician a preliminary

over-all view of the person and his major life problems. He should be able to formulate to himself his impressions as to the patient's general level of intelligence, emotional maturity or immaturity, the degree of his innate stability and the major stresses having a bearing on his present adjustment. If, on the other hand, the facts do not fall together into a picture that makes sense to him, he has every reason to ask for psychiatric consultation in order that the meaning and interpretation be clarified and his course of procedure be outlined. He is accustomed to referring unclear problems for specialty evaluation. The psychiatrist can serve the same function. In one or a few visits the psychiatric consultant can orient him to the problem and permit him to carry on unaided. Some patients will have simple problems that he can manage alone. Others may be more complex and require psychiatric evaluation. In still others therapy is best carried out jointly by internist and psychiatrist. In involved neurotic reactions, the therapy should be turned over to the psychiatrist.

Having ascertained these facts, what specifically can the practitioner hope to do about them? Pre-eminently he may decide upon one of two procedures to help the patient rid himself of his crippling anxiety or to help him deal with it constructively and perhaps to wall it off. This he will do in two main ways: by helping to modify the unbearable situations of life or by attempting to modify the patient so he can better tolerate the unbearable situation. Both procedures are included in what is called psychotherapy. Let us examine this in more detail.

The practitioner may have found that the patient is faced with very real difficulties in his contemporary life. When these can be changed or alleviated they should be. This may involve working with the family, to give them understanding of the illness, to relieve their anxiety about the sick person, to give them confidence in the therapist's attempt to cure the illness, to discuss the problem of the tangled emotional relations with husband, wife, or parents, to help relatives to avoid over-indulgence or over-severity, to act as marital counselor, to help with problems of emancipation, to act as impartial arbitrator in family disagreements or to counsel in the sexual problems of husband and wife to the end that both have mutual satisfaction. Today fourth year medical students are discovering how enlightening a visit to the home of their patient may be in revealing attitudes, tensions and social-economic factors that bear upon the illness. A brief history from a close relative may

throw additional and revealing light upon the patient's problem

Much can be done too in analysis and correction of unhappy, stressful work and school adjustments. Employers need interpretation and are avid for it as is witnessed by the rapid growth of industrial psychiatry. They usually welcome help in arranging work assignments and in understanding the workers' problems and needs. The physician can go far in actual arranging of a better and more appropriate work or school placement. If he is in doubt of what to advise, he can get professional help through employment counselors. It should be remembered that overwork rarely causes neuroses, although overwork at uncongenial tasks may aggravate it. Overwork is far more often the symptom of neuroses.

Where economic and social privations play a leading role, the physician can get help through the many social agencies in his community, the existence of which he is usually little aware. More importantly he needs to remember every human being functions best within a framework of work, play and relaxation which must be balanced. Attention to such simple needs can bring much relief—such things as the insistence upon regular exercise, vacations, rest, time for relaxation, the necessity of ending each day of work with a mind closed to the task until the next morning. He may prescribe play—a movie, or social evening or bowling, if need be. Many a patient has found in a sustained hobby an abiding relief from tension and daily strain. It is better than sedatives. Activity is important, bed rest and unearned vacations accomplish little in the neurotic. Specific principles of relaxation can be taught the patient—self-induced muscular relaxation, vigorous exercise of a non-competitive variety (swimming or riding, not golf or tennis), prolonged warm tubs, showers, massage, steam baths. The temporary use of sedatives can be used for emergency situations. The hygiene of sleep habits can be inculcated.

In brief, where obvious unbearable stresses exist in the actual contemporary life, they should be alleviated when feasible and practical. Suggestions are in order, but it is well to avoid too much regulation. The wise course is to help the patient come to his own decisions and choices regarding major or critical changes in his way of life, and to adhere to this no matter how much the patient pleads for the physician's authoritative decisions.

Situational relief of the kind prescribed, while important, may be

unfeasible or may be at best partial procedure. Far more important is the effort to help the patient achieve inner security, freedom from anxiety and an enhanced capacity to meet the actual stresses. This is pre-eminently the talking therapy, psychotherapy in its more specific sense. The aim of this is to have the patient talk out, get verbal catharsis, release, get his "problems off his chest" with the aim of gaining greater understanding of his emotional life and difficulties, so that he may manage himself more wisely and free himself of his crippling anxiety. In the process, the physician will listen more than he will talk. This can hardly be stressed too much. He must learn how to sit and just listen and he must forego the pleasure of hearing his own voice in order that his patient may freely have the time and freedom to say what is in him. He will invite full expression, and he will note whether talking brings genuine relief or merely upsets the patient. He will be guided in how far he can go and what topics to discuss by these observations. His task is not to dig out confessions, or premature discussion of sexual experiences, or to delve into unconscious motivations. His aim is to create an atmosphere of trust and confidence wherein the patient will spontaneously bring into the discussion his sensitive, anxiety-laden experiences, memories and phantasies. As the history unfolds he will recognize that contemporary problems always have their prototype in earlier patterns of emotional feelings, habits, and difficulties, particularly as they relate to childhood developments, the powerful family constellations and the prevailing habits of response to family members. It is surprising indeed how quickly and spontaneously the contemporary difficulties give way to the discussion of the early life with the heavy emphasis on the feelings and emotions experienced toward parents and brothers and sisters. With this recognition by the patient that he is transposing early feeling tones and traumatic emotions to contemporary people and situations, there may come a degree of insight that brings automatic relief from the present distress. More importantly the healing comes automatically with the talking and the sharing with the understanding physician.

Some degree of explanation to the patient of these mechanisms may be needed. Similarly explanations of the nature of his symptoms and how they are expressive of emotions may have to be given. The patient has to be taught these simple, to us self-evident, psychosomatic relations. They can be taught him by simple analogies, the somatic responses to talking in public, or to taking an examination, and he must then be



brought to see the relation of his symptoms to the emotions he has been discussing. This is easier if he can be shown that increase in discomfort commonly occurs when he is in a situation of particular stress. This process is what is meant by the technical term "explanation."

Hand in hand goes the need for reassurance. Here the physician's authoritativeness and the patient's confidence gained through sharing are of prime importance. The physician needs to be sure of his negative physical findings to be convincing. He needs to have performed the necessary physical examinations himself. The findings of some previous physician will not suffice. The patient wants the reassurance of his therapist's examination and findings. Such reassurance may be necessary repeatedly in a frightened patient, but it should not be overdone lest it defeat itself by false and hearty optimism. It is more effective when offered sparingly and thoughtfully than too frequently and glibly. Properly used, it is a powerful and necessary tool, for it is the voice of authority and protectiveness. The physician should not promise too much, lest he lose face when the promised results do not occur. Once the physical status is settled, it should not be reopened unless for new somatic indications, for it may raise doubts of the physician's competence or certainty and undo all that has been accomplished.

This technique of reassurance may require added persuasion—persuasion that the physician is right, that the patient must relinquish his problem to him, and that the symptom must be given up. This is particularly true if the secondary gain of illness is great, i.e., where the patient enjoys his illness, profits by it in over-attention, sympathy or love, or finds it financially profitable in insurance or compensation. Persuasion may need to be more positive, strong suggestion, or direction, or even implied command. The psychiatrist's most persuasive tool of suggestion is hypnosis. He may use it to suggest or command the disappearance of a hysterical symptom. Frequently too, the kindly ignoring of the actual symptom is indicated. Suggestion must be recognized as a powerful weapon. Any medicine is more effective if it is given with confidence and assurance that it will work. Even the placebo which has no place in psychiatry can work miracles. To prescribe medicine with the formulation "this medicine has helped many of my patients. I feel confident it will help you" may bring about remarkable improvement. It should be warned however that suggestion is apt to be brief-lived in its effect and is only a temporary measure to carry over while

more effective psychotherapy is being pursued

The physician's increasing and full knowledge of his patient will inevitably sum up in his own mind as the need for re-education. He will see how the personality is poorly balanced, how too much conscientiousness cripples performance, how excessive guilt feelings lead to insecurity and inadequacy, how foreboding anticipation cripples adventuresomeness, how habits of shyness, inarticulateness, distrust, exclusive self-preoccupation and lack of concern for others handicap social relations and friendships, how life-long attitudes of submission or aggression, temper or withdrawal interfere with the fullest realization of the patient's potentialities. These call for actual re-education, education in principles of normal health and behavior. Strength and courage and new direction will come to the patient mainly in proportion to what he can express and share with the physician. Haunting memories lose their stigma, fears and anxieties are relieved through desensitizing. The long haunting worry about masturbation disappears when it is understood as a developmental phase in every normal person's life. Similarly other anxieties lose their charge through discussion.

In performing this therapeutic function, the physician may be little able to verbalize, formulate or follow the steps in the process. It matters little whether he knows he is using techniques of explanation, reassurance, persuasion, suggestion, or re-education as long as he serves the function. Few psychiatrists and fewer patients can give logical verbalization to what has happened during the relationship and therapy. The pragmatic test of relief is what really matters.

War has heightened our appreciation of the amount of help and understanding that can be obtained from allied disciplines. The practitioner should inform himself of the excellent contributions made by the psychologist and the social worker since both are usually available in his community and they are ready to add their skills to his study. In the field of psychology extensive tests have been devised and proven to be of value in evaluating the kind and degree and severity of neurotic disability. Such tests as the Cornell Neurotic Index, the Rorschach Test, the Murray-Thematic Apperception Test for the determination of personality profiles, etc. A great variety of intelligence and aptitude tests are available for the better placement of individuals at work or in school.

The social worker is pre-eminently trained in the understanding of

individual, family and community problems and resources. The social worker's history will take the physician far in the understanding of the essential personality with which he is dealing. In turn she is ready for help in advising and finding of community resources for recreation, exercise, companionship, housing, special training, and job finding. These major contributions have long been left out of the curriculum of training of doctors. Slowly and fumblingly the average doctor stumbles across their usefulness. He would do well to obligate himself to know the full range of social work possibilities and cooperation.

Skill in therapy comes from experience. Experience involves continued study. A helpful literature for practitioners is beginning to accrue. To be recommended are such presentations as Binger's "The Doctor's Job,"<sup>1</sup> Dunbar's "Emotions and Bodily Change,"<sup>2</sup> Levine's "Psychotherapy in Medical Practice,"<sup>3</sup> Weiss and English "Psychosomatic Medicine,"<sup>4</sup> Menninger's "The Human Mind,"<sup>5</sup> Preston's "Psychiatry for the Curious,"<sup>6</sup> the publication "Psychosomatic Medicine." Other brief treatises of value are Whitehorn's "Guide to Interviewing and Clinical Personality, Study,"<sup>7</sup> R. Dicks' "The Ministry of Listening,"<sup>8</sup> Hamman's "Relationship of Psychiatry to Internal Medicine."<sup>9</sup>

From this simplified discussion, one would hope that the practitioner is convinced by now that all his patients will be improved by appropriate attention to their emotional life. Nothing that one can say so briefly will make the practitioner a psychotherapist. It may stimulate his desire to know more about the technique. If the doctor has achieved an attitude of tolerance towards these disabled people he will already have gained much. If he is determined to look for the emotional responses, even though they are not always evident or immediate, he is on the right track. This appeal is made that practitioners and psychiatrists work together for better medical care of human beings. It is an appeal that we go forward together in an educational venture wherein both of us can profit. Let us at least begin the process of study and acquisition of knowledge since only through the increasing skill of the practitioner can there be any hope for relief for those patients who constitute the bulk of all medical liabilities.

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## EVALUATION OF EARLY POSTOPERATIVE ACTIVITY\*

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SCIENTIFIC inquiry into the physiology of inactivity and the application of this knowledge to the problems of convalescence and rehabilitation are two of the prominent contributions of the war effort to medicine and surgery. The physiologic effects, biochemical alterations, and psychologic changes in the human economy which occur with prolonged periods of rest in bed have been ably discussed by Dr. Barr. My remarks will be limited to the practical evaluation of early activity after major surgical operations.

Such a regimen is not new. Early postoperative mobilization was first instituted by Emil Ries<sup>1</sup> who observed in 1899 "that after intra-abdominal work done by the vaginal route patients could be fed like perfectly healthy persons and could be allowed to be up and walking about in a remarkably short time—that the period for which it was advisable to confine such cases to bed could be counted by hours instead of days." Encouraged by his success with this regimen after vaginal celiotomy the same routine was shortly utilized in the management of patients following abdominal laparotomy. Early postoperative walking was also adopted by Boldt,<sup>2</sup> a former gynecologist of this city, and by 1906 these two authors had a combined series of nearly 900 patients who had been allowed up and about on the first or second day after laparotomy with "not a single instance of untoward result which could in any way be attributed to the early rising from bed."

An accelerated postoperative regimen was likewise advocated in many continental clinics<sup>3</sup> but was accepted less readily in England and America. Recently, however, due in part to the exigencies of military surgery and the urgent demands upon civilian hospitals, attention has once again been focussed upon the importance of early rehabilitation,

\* From the Department of Surgery of the Mary Imogene Bassett Hospital Cooperstown New York. Given October 10, 1945 before the Eighteenth Graduate Fortnight of The New York Academy of Medicine.

and modern surgeons who have had experience with this method of postoperative management comment favorably on their results.<sup>4,11</sup> Extensive bibliographies have been published by Smith,<sup>11</sup> Newburger,<sup>3</sup> and Leithauser.<sup>9</sup> The English and foreign literatures now embrace references to well over 10,000 patients who have been out of bed and walking on the first day after surgical operations of major magnitude and to many times this number who have become ambulatory on the second, third, fourth, and fifth days. Unfortunately, these papers often present no precise definition of "early activity" and with few exceptions the conclusions of the authors have been drawn from clinical impressions rather than comparative, statistical data. Hence, in order properly to evaluate early postoperative activity, it is imperative first to define the term, secondly to decide on certain measurable data upon which such an evaluation may be based, and thirdly, with these data in mind to compare the results of "early activity" with those of "late activity" among groups of patients sufficiently large to be of statistical significance.

*Definition* In this report "early activity" connotes arising from bed, standing, walking, and sitting in a chair on the *first* day after operation.

*Basis for Evaluation* The data upon which this evaluation is based include measurements of vital functions (temperature, pulse rate, blood pressure, vital capacity) indicative of the well being of the patient, reveal deviations from his usual dietary and gastrointestinal habits, disclose degrees of comfort or discomfort due to pain as measured by the administration of morphine, embrace a detailed analysis of the postoperative complications, and finally indicate clearly when normal activity is resumed.

*Presentation of Data and Comparison of Results* Series of observations on three groups of unselected patients which form the basis of this evaluation of early postoperative activity are herewith presented (Figure 1).

One hundred patients used as controls in the column designated "late postoperative activity" and 100 in the group termed "original early activity" who were ambulatory on the first postoperative day were discussed at the Symposium on the Abuse of Rest in Chicago at the Ninety-Fourth Annual Session of the American Medical Association in 1944.<sup>7</sup> These two groups each embrace thirty-nine hernioplasties, twenty-two appendicectomies for acute appendicitis, fourteen operations on the biliary tract, and twenty-five cases of abdominopelvic surgery (Figure

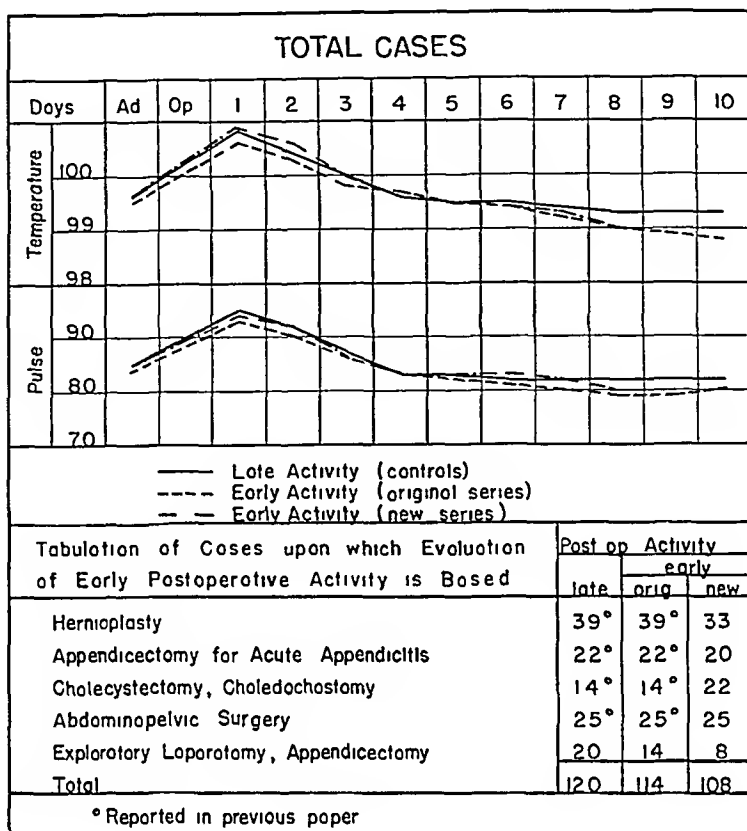


Figure 1 In the lower half of the chart are tabulated the cases upon which this evaluation of early postoperative activity is based. In the upper half are presented graphic records of the highest average daily temperature and pulse rate of all the patients in each group.

1) Patients subjected to these four well standardized operative procedures were originally chosen for comparative study because the total periods of hospitalization and convalescence after each were fairly well established by tradition. In the present study these groups have been respectively augmented by twenty and fourteen patients subjected to laparotomy and appendectomy for abdominal pain, and an entirely new series has been added. This embraces 108 patients upon whom the same operative procedures were performed, who were out of bed and walking on the first postoperative day, and whose convalescences thereafter were accelerated even more rapidly than those of the patients who comprised the original series. These cases are tabulated in the column designated "new early postoperative activity."

The average ages of the patients in the three groups were quite

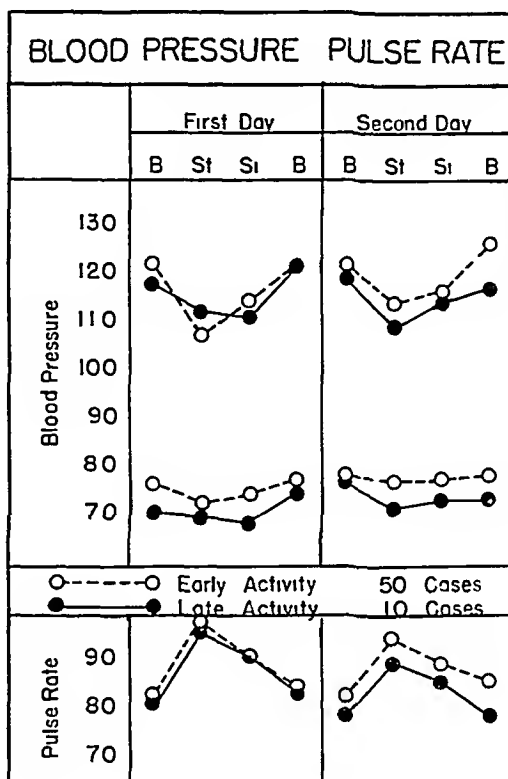


Figure 2 Curves indicating average changes in blood pressure and pulse rate coincidental with standing and sitting in a chair on the first and second days of activity among 50 patients who were ambulatory on the first postoperative day compared with similar observations on 10 patients who remained recumbent for 1-3 weeks after operation

comparable (Figure 5) Those in the control series ("late postoperative activity") remained in bed an average of 12.3 days while the patients in each of the other two groups were up and walking on the first postoperative day Those who comprised the foremost group remained in the Hospital for an average period of 15.4 days each, those in the original series of early activity for an average of 10.1 days, while the patients in the new series were hospitalized for 8.4 days only Occasional individuals in this group who lived within a radius of 12-15 miles from the Hospital were allowed to go home on the second, third, or fourth postoperative day to return to the out-patient department for removal of sutures No ill effects were observed when this freedom of activity was permitted



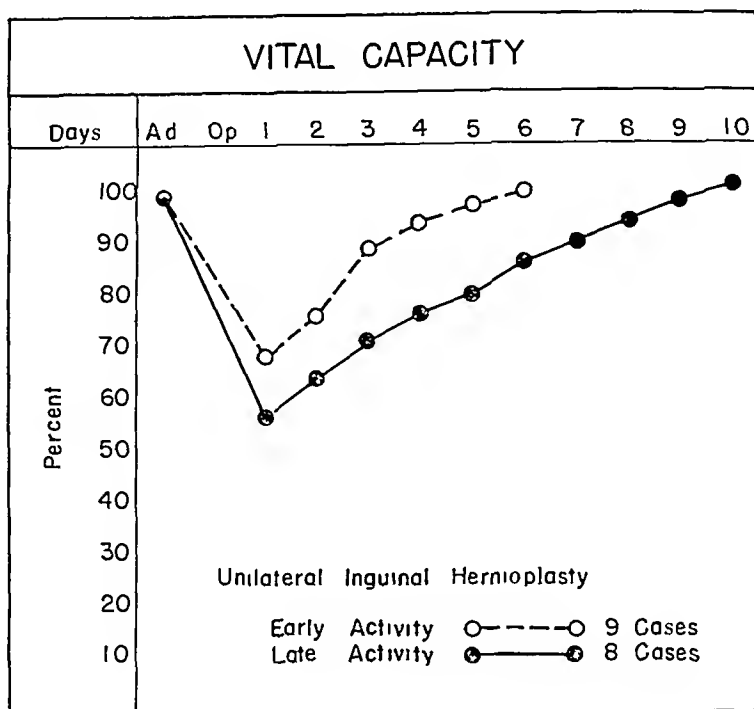


Figure 3 Composite curves representing the vital capacity of 9 patients who were ambulatory on the first day after unilateral inguinal hernioplasty and 8 patients who remained in bed for 12 days

*Temperature and Pulse Rate* Presented in Figure 1 are curves representing the composite temperature and pulse rate before operation and during the early convalescence of the patients in all three groups. These were plotted by averaging the highest levels recorded for every patient in each group on each day, and thus represent maximal elevations during the convalescent period. It is apparent from these curves that early postoperative activity does not affect adversely these indices of vital functions.

*Blood Pressure* In order to evaluate changes in blood pressure and pulse rate coincidental with early and late activity, two exactly comparable series of observations were made on fifty patients who were up on the first day and on ten who remained flat in bed for 7-21 days after operations of similar type. These observations were taken on both the first and second days of activity and comprised determinations of the blood pressure and pulse rate with the patient in bed, again immediately after standing erect on the floor, thirdly after sitting in a chair

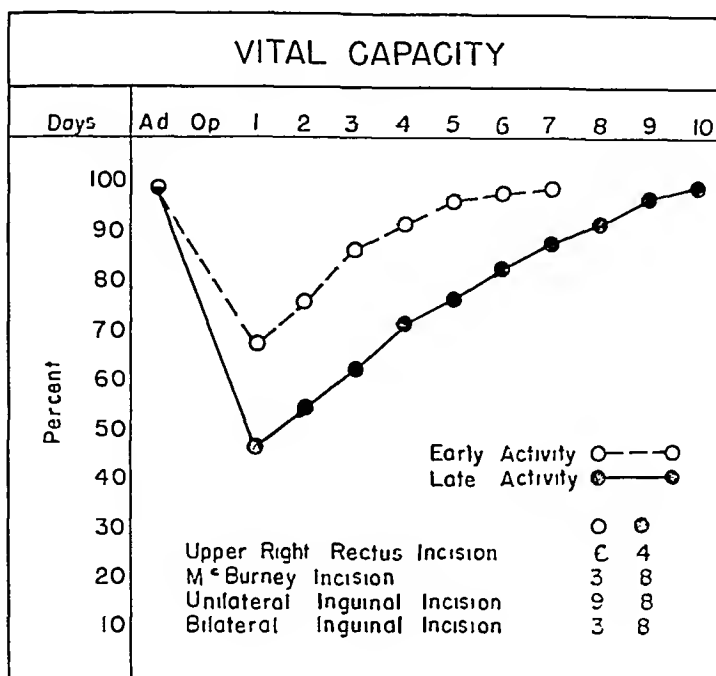


Figure 4 Similar curves for 21 patients who were up and walking on the first postoperative day after various procedures compared with 28 who remained in bed for the traditional convalescent periods following operations of similar type

for 10 minutes, and finally after return to bed. The results are plotted graphically in Figure 2. They indicate no greater drop in blood pressure or rise in pulse rate coincidental with the first two occasions of arising from bed after operation, when these be on the first and second post-operative days instead of after the lapse of 1-3 weeks in bed.

Immediately after standing minor changes occurred among the patients in each group, were still present though less marked after 10 minutes in a chair, and disappeared promptly upon return to bed.

Weakness, vertigo, mild syncope, nausea and sometimes vomiting occurred singly or in combination among 40 per cent of the patients who stood on the first postoperative day, similar reactions to the erect position were present among 75 per cent of the patients in the control group who did not stand until 1-3 weeks after operation

*Vital Capacity* Postoperative changes in vital capacity secondary to upper right rectus, McBurney, unilateral, and bilateral inguinal incisions have previously been reported for patients who remained in bed the traditional periods of time after operation<sup>12</sup> Herewith recorded are

ADDITIONAL DATA	<i>Post op Activity</i>		
	<i>Late</i>	<i>Early</i>	
		<i>Orig</i>	<i>New</i>
Number of Patients	120	114	108
Average Age	35 8	41 0	37 8
Days in Bed after Operation	12 3	1 0	1 0
Days in Hospital	15 4	10 1	8 4
Weeks of Convalescence	10 0	5 8	4 5
Days before Resumption of Normal Diet	8 7	5 2	3 3
Average Loss of Weight per Patient	3 8	3 0	4 5
Morphine Average Amount per Patient	0 062	0 029	0 027
Number of Doses per Patient	5 6	2 6	2 6
Incidence of Postoperative Distention	50 5%	26 2%	22 0%
Incidence of Gas Pains	69 4%	37 9%	28 9%
Patients requiring Poultrice and Rectal Tube	61 3%	41 2%	32 7%
Average Number per Patient	2 5	1 1	0 6
Patients requiring Enema	90 0%	63 4%	53 4%
Average Number per Patient	2 5	0 9	0 7

Figure 5 Tabulation of additional data of significance in the evaluation of early postoperative activity

similar determinations on nine patients who were ambulatory on the first postoperative day after unilateral inguinal hernioplasty (Figure 3) and on twenty-one patients who were up and walking on the first day after this and other operative procedures (Figure 4). For comparison as controls are plotted curves from the previously published observations. All determinations were made with the patients supine and represent the highest of 3-5 readings. For the sake of uniformity the preoperative levels in each case have been considered as 100 per cent and the subsequent changes are plotted on a percentage basis.

From these charts it is obvious that the drop in vital capacity which follows immediately in the wake of major surgical operations is less precipitous and pronounced and the return to normal more prompt among patients who are ambulatory on the first postoperative day than among those who remain recumbent and inactive for 10-14 days.

*Diet* Subsequent to the publication of the second paper on early postoperative activity a letter was received from Captain William A. Barrett,<sup>13</sup> 100th Evacuation Hospital, Belgium, which, in part, read as follows: "For over two years I have allowed ambulation on the first day following all elective operations with the same beneficial effects you observed. All these patients likewise had a regular diet postoperatively."

except for the first meal which was toast and tea or bouillon. Invariably they tolerated a regular diet at the succeeding meal. When this procedure is followed there are no 'gas pains' and a negligible loss of weight." Captain Barrett's experience was confirmed in this clinic. Many ambulatory patients expressed a desire to "have more to eat" on the second, third, and fourth postoperative days. Consequently, the dietary routine for those in the new series without complications was accelerated to permit hot clear fluids on the first postoperative day, soft diet on the second, and regular diet on the third. The incidence of postoperative distention and "gas pains" was appreciably lowered as indicated in the next paragraph but the average loss of weight per patient in this group was slightly greater than in either of the others. If this weight loss be significant, the reason is not apparent.

*Gastrointestinal Function* Due in part to early postoperative activity and doubtless also to more and more prompt resumption of a normal diet the occurrence of postoperative distention decreased from 50.5 per cent among the recumbent patients in the control group to 26.2 per cent among those in the original group of early activity and 22.0 per cent among the patients in the new series (Figure 5). The incidence of "gas pains" likewise fell from 69.4 through 37.9 to 28.9 per cent among the patients who were ambulatory on the first day and were permitted a regular diet on the third postoperative day.

The number of individuals who required abdominal poultices and rectal tube for the treatment of distention and those who demanded one or more enemas for evacuation of the large bowel after operation decreased very appreciably (Figure 5). The actual number of enemas administered fell from an average of  $2\frac{1}{2}$  to each patient of the control group to 1 per patient in the original series and to 1 for every other patient in the new group.

*Pain* If the amount of morphine required for the control of pain be accepted as an index of the amount of discomfort suffered by the patient, it is at once apparent that those who were ambulatory on the first postoperative day were more comfortable than were those who remained recumbent for 12 days. The patients in the two active groups required less than half as much morphine and fewer than half as many doses as did those in the control group (Figure 5). Seldom was any hypodermic necessary after the first few hours following recovery from anesthesia.

POSTOPERATIVE COMPLICATIONS				
Complication		<i>P O Activity</i>		
		<i>Late</i>		<i>Early</i>
		<i>Controls</i>	<i>Orig</i>	<i>New</i>
<i>Local</i>	Disruption of wound	0	0	0
	Subsequent Herniation	3	1	0
	Recurrence of Hernia	2	0	1
	Infection of Wound	0	1	2
	Hematoma in Wound	1	2	0
	Silk or Cotton Sinus	1	0	1
	Residual Intraperitoneal Abscess	2	0	0
<i>Pulmonary</i>	Massive Atelectasis	1	0	0
	Partial Atelectasis	0	1	2
	Bronchopneumonia	3	1	2
	Infarct of Lung, embolic	1	0	2
	Suspected Infarct of Lung	1	0	1
	Serious Pleurisy	0	0	1
	Bronchitis	1	2	1
	Nasopharyngitis	2	0	0
<i>Cardiac</i>	Coronary Thrombosis	1	0	0
	Angina Pectoris	1	0	0
	Paroxysmal Auricular Fibrillation	1	0	0
<i>Vascular</i>	Iliofemoral Thrombophlebitis	1	1	1
	Thrombosis of Deep Veins of Legs	1	0	1
	Suspected Thrombosis	3	1	5
<i>Genito-urinary</i>	Inhibition of Bladder			
	Requiring one catheterization	8	7	9
	Requiring several catheterizations	19	3	9
	Cystitis due to E. Coli	1	0	0
	Uremia	0	0	1
<i>Gastro-intestinal</i>	Dilatation of Stomach	3	0	0
	Fecal Impaction	3	0	1
<i>General</i>	Unexplained Fever	6	0	0
	<i>Total</i>	66	20	40
	<i>Average</i>	0.55	0.17	0.36
	<i>Incidence</i>	55%	17%	36%

Figure 6 Tabulation of postoperative complications incidental to early and late activity

Individuals who had previous operations were uniformly enthusiastic about early activity. Without exception, each one stated that arising from bed and walking were accompanied by less pain and discomfort on the first postoperative day than after 10-15 days of recumbency. Furthermore, the subsequent convalescence was likewise much more comfortable throughout.

*Postoperative Complications* All patients have been observed carefully and examined frequently for evidence of complications during the convalescent period. These have been classified according to the system involved and tabulated in Figure 6.

If early postoperative activity is to be correctly evaluated it is imperative that meticulous attention be paid to symptoms and signs which suggest some complication even though its actual existence may be only suspected.

No wounds disrupted. Subsequent herniation in abdominal incisions and recurrence of hernia after repair were both more common among the patients who remained in bed. The 3 infected wounds were not related to early activity, 2 were operative mishaps and 1 was due to contamination by a gangrenous appendix.

The speaker has never believed that pulmonary and vascular complications were so thoroughly eradicated as has been quoted by previous writers, "1,569 cases, 3,197 cases without complications, 6,000 patients out of bed on the first postoperative day with not a single case of embolism."<sup>9</sup> This opinion is substantiated by the incidence of such complications among the ambulatory patients of the most recent group submitted to analysis (Figure 6). The etiology and pathologic physiology of postoperative pulmonary and circulatory complications have been discussed elsewhere<sup>7</sup> and will not here be repeated. However, the speaker wishes to emphasize the opinion that elevation of the foot of the bed 8-10 inches, hourly exercises of the lower extremities, and early postoperative walking may circumvent the formation and liberation of thrombi of sufficient size to precipitate a fatal postoperative catastrophe.

Genito-urinary complications, particularly the necessity for repeated catheterizations, gastrointestinal difficulties, and fever of undetermined origin were more common among the patients who remained in bed for 12 days after operation.

The total number of complications was likewise much higher among these patients of the control series than among those in either of the active groups and the incidence of complications was double their collective incidence among both groups of patients who were out of bed and walking on the first postoperative day (Figure 6).

*Weeks of Convalescence* The convalescent period is considered as beginning with the first postoperative day and continuing until the patient resumed full activity at the employment which was interrupted.

SUTURES	<i>Post op Activity</i>		
	<i>Late</i>	<i>Early</i>	
		<i>Orig</i>	<i>New</i>
Silk	87	99	24
Cotton	0	0	77
Catgut	10	7	4
Silk and Silver Wire	1	0	0
Cotton and Silver Wire	0	0	1
Catgut and Silver Wire	1	5	0
Silk and Silkworm Gut	3	0	1
Cotton and Silkworm Gut	0	0	1
Catgut and Silkworm Gut	1	1	0
Silk and Fascia	0	1	0
Not Stated	17	0	1
Total	120	114	108

Figure 7 Tabulation of materials used for sutures

by admission to the Hospital for surgical treatment. Among the patients herein discussed the period of convalescence was reduced from 10 weeks to 5.8 weeks in the original series and to 4.5 weeks in the new series by early postoperative activity and walking (Figure 5). This represents a cut of 55 per cent in time formerly devoted to convalescence and suggests that the period of inertia which traditionally follows in the wake of surgery may be largely eliminated.

#### FURTHER COMMENT

*Sutures.* Many authors who have had experience with early postoperative activity have emphasized the superiority of one type of material for sutures over all others<sup>4, 5, 8, 10, 11</sup>. In Figure 7 are tabulated the various materials which were utilized in the cases herein discussed. Silk and cotton were used most frequently, catgut alone and in combination with non-absorbable supporting sutures was employed less often. No disruptions occurred. With the exception of three infections (an incidence of 0.8 per cent), one transient silk and one cotton sinus, all wounds healed by first intention.

Scrupulous care in the prevention of infection, meticulous hemostasis, gentle manipulation and accurate reapproximation of tissues layer by layer with fine interrupted sutures are doubtless much more im-

ANESTHESIA	Post op Activity		
	Late	Early	
		Orig	New
Local Novocaine	7	16	4
Novocaine, Nitrous Oxide, Oxygen	5	0	0
Spinal	16	11	15
Continuous Spinal	0	2	0
Spinal and Local Novocaine	0	1	1
Spinal, Nitrous Oxide, Oxygen	5	6	2
Spinal, Nitrous Oxide, Oxygen, Ether	1	0	3
Nitrous Oxide, Oxygen, Ether	43	17	19
Avertin, Nitrous Oxide, Oxygen	6	19	24
Avertin, Nitrous Oxide, Oxygen, Ether	37	41	40
Avertin and Ether	0	1	0
Total	120	114	108

Figure 8 Tabulation of anesthetic agents employed

portant than the type of material used

*Healing* During the early days of modern surgery absolute rest and protection were considered so essential for the proper healing of wounds that immobilization for 3-4 weeks in a plaster spica was often employed after repair of an inguinal hernia. With the realization that tissues which are continuously and repeatedly in motion heal kindly, that the wounds of infants and children who cannot be kept quietly in bed after operation likewise heal firmly in spite of activity, opinions have gradually changed and immobilization is no longer considered essential for the proper healing of coapted tissues. In fact, Newburger<sup>14</sup> and Kimbarovskiy (quoted by Leithauser<sup>9</sup>) believe that healing is accelerated by activity.

In the cases herein reported incisional herniae and recurrent herniae were less common among the ambulatory patients than among those who remained at rest in bed for the traditional postoperative period of recumbency.

*Anesthesia* Early postoperative activity and walking are neither limited or contraindicated by the type of anesthesia employed. The various agents utilized in the three groups of cases are tabulated in Figure 8.

*Additional Cases* The cases included in the above study represent



consecutive unselected patients who were submitted to the five operative procedures enumerated in Figure 1. These were chosen because the period of rest in bed, the days of confinement to the Hospital and the total duration of the convalescence after each were well established by tradition. Any deviation therefrom attributed to early postoperative activity could be readily evaluated. Less easily evaluated because less amenable to comparative analysis and hence not included in this presentation are many patients who have also been ambulatory on the first day after many other types of operative procedures of major magnitude. These include operations on the esophagus, resections, closure of perforations, and other operations on the gastrointestinal tract and colon, nephrectomy and other procedures on the kidney and ureter, prostatectomy by the suprapubic and transurethral routes, subtotal thyroidectomy, and radical mastectomy. In fact, with very few exceptions all patients are now ambulatory on the first postoperative day.

*Contraindications* There are very few absolute contraindications. Generalized bacterial peritonitis, debility and weakness of such degree that the patient is unable to stand even with assistance, serious bleeding at the operating table or shortly thereafter, thyroid crisis, immediate or early postoperative coronary thrombosis, and non-fatal pulmonary embolism are definite contraindications to early ambulatory activity.

Fever, pulmonary complications other than infarction due to embolus, chemical peritonitis, intraperitoneal abscess, abdominal distention, draining wounds and sinuses, and tubes in hollow viscera so placed either by operation or through natural channels are not contraindications.

Thrombosis in the deep veins of the legs should be treated by prompt interruption of the venous channel proximal to the clot after which the presence of the thrombus should not be considered as a contraindication to postoperative activity.

### CONCLUSION

Early postoperative activity, walking, and other accelerated modifications in customary convalescent care provide safe innovations in postoperative management by which the process of deconditioning may be largely eliminated and early rehabilitation achieved. The data submitted above in evaluation of this program support these conclusions.

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BULLETIN OF  
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FEBRUARY 1946

PHYSIOPATHOLOGY AND SURGICAL  
TREATMENT OF CONGENITAL  
CARDIOVASCULAR DEFECTS\*

*Harvey Lecture, November 15, 1945*

ALFRED BLALOCK

Professor of Surgery and Director of the Department of Surgery The Johns Hopkins University  
and Surgeon in Chief, The Johns Hopkins Hospital

THE fame of William Harvey is of the enduring type that increases with the passing of years. It was my privilege to be present in London in 1928 at the tercentennial celebration of the discovery of "the movements of the heart and blood." Undoubtedly others in this audience were equally fortunate and departed, as did I, with an even more profound respect for the great anatomist and physiologist of the seventeenth century. The objectives of the Harvey Society are not limited to the diffusion of scientific knowledge in selected subjects in anatomy and physiology but are extended to include pathology, bacteriology, pharmacology, and physiological and pathological chemistry—to the alterations which take place as the result of both structural abnormalities and disease. In this Harvey Lecture it gives me a sense of gratification to discuss certain abnormalities of the circulation, the normal physiology

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of which was first established by Harvey himself, and to outline the recent advances which have been made in the surgical treatment of these conditions

Congenital cardiovascular defects are not rare in infancy, and it is only because of the high early mortality rate that the incidence after the age of twelve years is low. The complex nature of the defects, which adds to the difficulty of diagnosis, particularly in infants, and the lack of successful therapeutic methods resulted for years in a general neglect of this field. It is only in recent years that greater interest has been aroused as a result of the work of Maude Abbott, Taussig, Gross, Burwell and others. Their investigations have shown that it is no longer adequate simply to differentiate congenital from acquired heart disease. In a large percentage of cases one should be able to diagnose the particular defects which are present. Advances in surgical therapy for certain types make it all the more important that these types be recognized. That the advances are recent is shown by the statement in the 1937 edition of "Heart Disease" by White<sup>1</sup> to the effect that "there is no curative treatment, surgical or medical, for congenital cardiac defects."

Maude Abbott<sup>2</sup> devised a clinical classification of congenital heart disease in which the patients are divided into three groups. The first group includes those without abnormal communications or shunts between the right and left sides of the heart. Cyanosis is not a part of the picture. This group includes patients with simple dextrocardia, anomalies of the pericardium, primary congenital hypertrophy of the heart, pure subaortic or aortic stenosis, pure mitral stenosis, and coarctation of the aorta. The second group embraces patients with arteriovenous shunt in whom arterial blood enters the pulmonary circulation. Cyanosis is usually not observed. There is, however, possible terminal or transient reversal of flow with cyanosis due to the entrance of venous blood into the systemic circulation. Patients in this second group have defects of the interauricular septum, defects of the interventricular septum, localized defects of the aortic septum, and patent ductus arteriosus. This is the potentially but rarely cyanotic group. The third group according to Abbott includes those patients in whom cyanosis associated with the entrance of venous blood in large quantities into the systemic circulation is a prominent feature. Included among the many causes are defects of the interventricular septum with dextroposition of the aorta, tricuspid stenosis, tricuspid atresia with septal defects, transposition of arterial

trunks with defects of the ventricular septum, persistent truncus arteriosus, and the tetralogy of Fallot

It happens that advances in surgical therapy have been made in a representative of each of the three groups described by Abbott—coarctation of the aorta in the acyanotic group, patent ductus arteriosus in the usually acyanotic but occasionally cyanotic group, and pulmonic stenosis (usually the tetralogy of Fallot) in the cyanotic group. This lecture will consist in the main of a consideration of patent ductus arteriosus, of coarctation of the aorta, and of the tetralogy of Fallot with particular emphasis on the latter condition.

### PATENT DUCTUS ARTERIOSUS

Although a procedure for closure of patent ductus arteriosus had been described by Munro<sup>3</sup> in 1907 and although the operation had been attempted by Strieder,<sup>4</sup> the first successful closure of an open ductus was performed by Gross<sup>5</sup> in 1938. According to Abbott, patent ductus arteriosus occurs together with other congenital heart lesions twice as often as it is observed as a single abnormality. The impression that there is usually an associated lesion probably accounts for the years that elapsed between the initial description of the operative procedure and the successful undertaking by Gross. As regards the incidence of associated lesions it is likely that Abbott's statistics are misleading in that the figures were derived from autopsy material and probably represented an undue number of the more complicated conditions. Studies in the past six years have shown that patent ductus arteriosus frequently exists as an isolated lesion. It is estimated by Keys and Shapiro<sup>6</sup> that there are approximately 20,000 persons in this country with a patent ductus. Great credit is due Gross and Hubbard not only for the benefit accorded patients with patent ductus arteriosus but for the stimulus to further exploration of the problems of congenital heart disease. Gross originally considered bacterial endarteritis a contraindication to operation, and it is due to the work of Touroff<sup>7</sup> that this view has been altered.

The most extensive studies of the effects of patent ductus arteriosus on the circulation have been carried out by Eppinger, Burwell and Gross.<sup>8</sup> These workers demonstrated that the blood flowed from the aorta to the pulmonary artery and not in the reverse direction, that the volume of the leak in patients with large openings constituted 45 to 75



per cent of the blood expelled by the left ventricle, and that because this large volume of blood returned to the left ventricle without passing through the right, the output of the left ventricle was two to four times that of the right. Keys<sup>9</sup> found that the leak may constitute from 20 to 70 per cent of the left ventricular output. Even though there are reasons for doubting the magnitude of the recorded alterations, it appears that the overworking of the left ventricle probably explains the primary occurrence of left ventricular failure when failure occurs.

The recorded studies on the circulation explain and support the clinical observation that patients with failure or diminished reserve are benefited by closure of an open ductus. They also indicate that closure of the ductus in the absence of signs of failure may protect the heart from an eventually disabling burden. It must be borne in mind, however, that many persons with a patent ductus never have any disability as a result of the abnormality. There is a difference of opinion whether operation is indicated for patients without symptoms. Advances in the chemotherapy of bacterial endarteritis make less urgent the necessity for ligating the ductus from a prophylactic viewpoint. It does appear, however, that closure of the ductus is indicated for a patient with an established infection whether it does or does not show a favorable response to the use of chemotherapeutic agents.

I shall speak briefly regarding methods for effecting permanent closure of patent ductus arteriosus. The first method used by Gross was that of simple ligation of the ductus. It is known that the lumen of a large artery which is closed by ligation in continuity may become patent again as the ligature cuts through the wall. It is not surprising that Gross abandoned this method after re-establishment of the fistula occurred in several of his first fourteen patients. The second method employed consisted of the use of cellophane in addition to the ligature. Despite the fact that cellophane produces scarring, the ductus reopened in several of the patients. The third method used by Gross<sup>10</sup> consisted of complete division of the ductus and closure of the two ends. During the past three years my associates and I have operated upon nineteen patients with patent ductus arteriosus, most of whom were referred by Dr. Helen Taussig. Various methods, including division and closure of the ductus, have been used. There has been only one patient in whom there was evidence that the lumen became re-established, in this case a simple ligature had been used. Although no unusual difficulties have been encountered, I

think that division and closure of the ductus is an unnecessarily dangerous operation. The method which we employ at the present time consists of (1) the careful exposure of the entire length of the ductus, (2) the use of a purse string suture ligature of silk at the aortic and pulmonic ends of the ductus, (3) the use of two through and through mattress sutures of silk between the purse string ligatures, and (4) the placing of a ligature of umbilical tape over the mattress sutures. There has been no evidence of reopening of the ductus in the seven cases in which this method has been used.

As I have stated previously, successful surgical treatment of patent ductus arteriosus has led to an increased interest in all types of congenital heart disease. My interest, however, in the next disorder to be discussed, namely coarctation of the aorta, was aroused as a result of experiments on another subject and a chance conversation with Dr. E. A. Park. In an attempt to produce pulmonary arteriosclerosis, Levy and I<sup>11</sup> in 1938 performed operations on dogs in which the proximal end of the severed left subclavian artery was anastomosed to the distal divided end of the left pulmonary artery. In other words, the systemic and pulmonary circulations were connected by a suture anastomosis. Some of these animals were followed for as long as six years after operation. Much to our disappointment, arteriosclerosis did not develop. The blood pressure in the pulmonary artery only a short distance beyond the point of anastomosis was less than half that in the systemic arteries. Except in instances in which partial thrombosis occurred at the anastomotic site, microscopic examination showed no noteworthy alterations in either the left pulmonary artery or the lung. During a discussion of these results with Dr. Park, he suggested that the principle of altering the course and function of a vessel might be used in the treatment of coarctation of the aorta.

### COARCTATION OF THE AORTA

Coarctation of the aorta is a narrowing of the lumen of the vessel of varying degrees in the vicinity of the insertion of the ductus arteriosus. It was found in 142 of Abbott's series of 1,000 cases of congenital cardiovascular defects. It was the primary lesion in 79 of these and was associated with other abnormalities in 63 cases. The commonest form of aortic coarctation is the so-called adult type in which there is a localized constriction of the aorta usually at or just below the insertion

of the ductus arteriosus. Less frequent but more serious is the so-called infantile type in which there is narrowing of a greater length of the aorta. Patients with this type usually die in early infancy.

The symptoms associated with coarctation of the adult type vary according to the degree of the stenosis and the extent of the collateral arterial pathways. There is usually no difficulty in diagnosis if one is acquainted with the difference between the arterial blood pressure in the arms and in the legs, the palpable pulsations in dilated collateral arteries, the notching of the ribs, and the systolic murmur transmitted down the upper spine. A considerable degree of coarctation usually results in cerebral hemorrhage, thrombosis, heart failure, rupture of the aorta, or bacterial endarteritis. It was because of the incapacity and the high mortality associated with stenosis of marked degree that the following experiments were performed.

The experimental problem which was undertaken was that of severing the aorta at the level of the obliterated ductus arteriosus, closing the two ends, and performing an anastomosis between the divided proximal end of the left subclavian artery and the side of the aorta distal to the point at which it had been divided. It is known that dogs will not survive total occlusion of the thoracic aorta in one stage if one relies only upon the usual collateral channels. The mortality rate under such conditions is 100 per cent. Hence, if survival should occur in our animals, it would mean that an appreciable quantity of blood was being conducted below the point of occlusion as a result of altering the course of the subclavian artery.

A total of forty-three experiments<sup>12</sup> were performed on dogs. Only ten of the animals survived the operation for several months or longer. There were six deaths in the first 24 postoperative hours. Fifteen of the animals lived for periods ranging from five to 25 days. The predominating postoperative complication was paralysis of the posterior part of the body. Limiting our consideration to the ten animals which survived the procedure for long periods, we note that six of these showed no paralysis at any time. Two of the animals had a slight weakness of the posterior extremities which disappeared in a few days. The pressure in the carotid and femoral arteries was determined from time to time. In each instance the arterial pressure in the carotid was higher than that in the femoral but in no case was this difference very great. It appears, therefore, that the flow of blood through the transposed subclavian

artery and the dilated collateral vessels was sufficient to prevent death in some instances of total aortic occlusion. Furthermore, it was found that hypotension of the posterior part of the body did not occur in the animals which survived. Further evidence that the transposed subclavian artery was an important pathway for conducting blood to the posterior part of the body was supplied by the one experiment in which the subclavian artery was divided nine months after the original operation. Paralysis of the posterior extremities developed and the animal died 24 hours after operation.

The mortality rate in these experiments and the high incidence of paralysis of the posterior extremities made us hesitate to recommend the use of this procedure in man. In discussing the results Dr. Park and I stated<sup>12</sup> "it would appear that the patient with a chronic partial occlusion of the aorta would tolerate a temporary complete occlusion better than the normal dog in which there has been no stimulus to the formation of collateral arterial pathways. In any case this procedure, or a modification of it, should be considered only in those cases of coarctation in which the outlook is very grave since many patients with coarctation of the aorta have a fairly long life expectancy." After the completion of this work several patients with coarctation of the aorta were studied, but the condition did not seem sufficiently grave to warrant the risk associated with operation. This circumstance was probably fortunate for it appears now that the procedure performed by Crafoord<sup>13</sup> in Sweden (October 19, 1944) and by Gross<sup>14</sup> in Boston (June 28, 1945) is a better one than that devised by Dr. Park and me. In this recent operation the stenotic area is excised and an end to end anastomosis of the two ends of the aorta is performed. Since the lumen of the aorta is considerably larger than that of the subclavian artery, the procedure employed by Crafoord and by Gross seems to be a better one than that which Dr. Park and I described. However, it may be necessary to use our method or a modification of it if the stenotic area is so long, as in the infantile type of coarctation, that the two ends of the aorta cannot be brought together if excision is performed. It is of interest that the method of Crafoord and of Gross when used on normal dogs frequently results in paralysis of the posterior extremities. This observation indicates again that the patient with coarctation is aided in withstanding temporary total occlusion of the aorta by the previous stimulus to the development of collateral pathways.

## PULMONARY STENOSIS AND PULMONARY ATRESIA

It was during a discussion of the experimental studies on coarctation of the aorta with Dr Helen Taussig that she expressed the opinion that patients with pulmonic stenosis or atresia would be benefited if a means could be devised whereby a greater volume of blood would reach the lungs. Thus we come to a consideration of the third and last group in Abbott's classification, the most prominent feature of which is cyanosis. This third group is a heterogenous one embracing various types of abnormalities. The most frequently encountered type is the tetralogy of Fallot, which is characterized by pulmonic stenosis or atresia, interventricular septal defect, dextroposition of the aorta, and right ventricular hypertrophy.

I have stated previously that cyanosis is usually present in patients with this and similar abnormalities. It is due to the presence of reduced hemoglobin in the circulating blood and is the visible manifestation of the underlying anoxemia and compensatory polycythemia. Lundsgaard and Van Slyke<sup>15</sup> stated that there are four important factors in the production of cyanosis, namely, (1) the total hemoglobin content, (2) the degree of oxygen unsaturation of the arterial blood coming from the aerated lung areas, (3) the proportion of blood passing from right heart to left through unaerated channels, and (4) the oxygen consumption in the capillaries. It has been found that the cyanosis of most patients, including many of those with congenital cardiovascular defects, can be definitely lessened by the prolonged inhalation of high concentrations of oxygen. The assumption that all of the blood which passed through the lungs was not fully oxygenated led some observers to believe that further increase in the circulation of blood to the lungs would result in no benefit. On the contrary, there are a number of reasons, which will not be repeated here, why patients with pulmonary stenosis or atresia might be benefited if the pulmonary blood flow was increased. Perhaps the most important evidence is supplied by the observation that the condition of children with pulmonary stenosis or atresia and with patent ductus arteriosus becomes worse if the ductus closes, thereby reducing further the flow of blood to the lungs. It is generally recognized by cardiologists that one of the dangers connected with the operative closure of a patent ductus lies in the possibility of an associated pulmonary stenosis, and it is for this reason that the effect of

temporary occlusion is tested before the closure is made permanent

Following the original suggestion of Dr Taussig some two years ago that a means be found for increasing the flow of blood to the lungs, I undertook studies on experimental animals. It was evident that there were two major problems, namely, (1) the devising of a technique by which the blood flow to the lungs could be increased, and (2) the testing of the method in animals with a high degree of unsaturation of the arterial blood

Technical methods by which the blood flow to the lungs might be increased will be considered first. There have been reported in the literature only 12 cases of chronic valvular disease in man in which attempts have been made by operative means to lessen the degree of stenosis. One of the patients had pulmonic stenosis, one had aortic stenosis, and the remaining ten had mitral stenosis. The methods which were used consisted of (1) incision of the stenotic area with a small tenotome knife, (2) dilation of the stenotic area with a finger, and (3) excision of a segment of the valve with a cardiovalvulotome. Seven of the ten operations for mitral stenosis were reported by Cutler and Beck<sup>14</sup>. In the first of these patients the stenotic area was incised with a tenotome knife. This patient survived for four and a half years and was believed to have been somewhat improved by the operative procedure. The other six patients reported by Cutler and his associates died shortly after operation. The same was true of the patients with mitral stenosis operated upon by Allen and Graham<sup>17</sup> and by Pribram<sup>18</sup>. Souttar<sup>19</sup> reported the survival of a patient in whom he dilated the mitral valve with his finger. The patient of Tuffier<sup>20</sup> in whom dilation with the finger was used in the treatment of aortic stenosis was said to be improved. Doyen<sup>21</sup> in 1913 reported his experience in the treatment of a patient 20 years of age with congenital pulmonic stenosis. A small tenotome knife was introduced into the right ventricle and an attempt was made to divide what was thought to be a stenotic valve. The patient died several hours later and examination showed narrowing of the conus rather than stenosis of the valve. Thus it is to be noted that only three of the twelve patients survived the operative procedure, two having had finger dilation of the mitral or the aortic valve respectively, and one having been treated by incision of a stenotic mitral valve.

It appears to be unlikely that an operation on the stenotic area itself would be successful in the treatment of congenital pulmonic stenosis

The defect is usually in the conus rather than in the valve. Even if one were able to increase the size of the opening by some safe means as yet undiscovered, the chances are that the stenosis would return gradually to the original condition. It was an appreciation of this fact and the previous experience in the anastomosis of the systemic and pulmonic vessels which led to the creation of an artificial ductus arteriosus in the experimental attempt to supply a greater volume of blood to the lungs.

The question arose as to the type of anastomosis which should be performed. A suture anastomosis between the aorta and the main pulmonary artery was excluded as a possibility because it would be necessary to interrupt the circulation for a longer time than is compatible with life. The branches of the aorta which are in such position that they might be anastomosed to one of the pulmonary arteries are the subclavian arteries, the carotid arteries, and the innominate artery. Either the right or the left pulmonary artery might be used. A further question was whether the end of the systemic artery and the side of one of the pulmonary arteries should be anastomosed or whether the end of the systemic artery should be joined to the divided distal end of one of the pulmonary arteries. The former method appeared to be the one of choice since it would allow the blood to flow to both lungs. It is, of course, the type of union which is present in patent ductus arteriosus.

Following these studies on technical means for increasing the flow of blood to the lungs, attention was devoted to attempts to produce in experimental animals the type of general disturbance which is present in the patient with pulmonic stenosis. Means are not available for reproducing in its entirety the tetralogy of Fallot. After unsuccessful attempts to cause cyanosis and anoxemia by several different methods, a high degree of oxygen unsaturation was produced by the removal of lobes of one or both lungs and the creation of pulmonary arteriovenous fistulas by the anastomosis of the proximal ends of the pulmonary artery and vein of the resected lobe or lobes. This operation caused some of the venous blood to return to the left side of the heart without passing through the pulmonary capillaries and resulted in varying degrees of oxygen unsaturation of arterial blood. The creation of an artificial ductus arteriosus under these conditions by the anastomosis of the proximal end of the subclavian or innominate artery to the side of one of the pulmonary arteries usually resulted in an increase in the oxygen saturation of the arterial blood. The presence of the artificial ductus allowed

some of the arterial blood which was only partially saturated with oxygen to pass through the lungs instead of continuing through the systemic circulation. While it was realized that the experimentally produced condition was a poor reproduction of that seen in the patient with pulmonic stenosis, the experiments at least supported the hypothesis that improvement would result if an artificial ductus was created.

Even after Dr. Taussig and I decided to attempt the operation on patients, there were three unknown elements which caused hesitation for some time before the initial operation was undertaken. The most troublesome questions were: Would an intensely cyanotic child tolerate a long operative procedure in which general anesthesia and the opening of one of the pleural cavities were necessary? Granting that the answer to the first question was in the affirmative, would the patient tolerate temporary occlusion of either the right or the left pulmonary artery for the time that would be required for making an anastomosis by suture? Would ligation and division of the subclavian artery result in serious impairment of the circulation to the arm? It was apparent that the answers could be supplied only by making the clinical tests. The situation was discussed frankly with the parents of the children who were chosen for operation. A number of distressing complications have been encountered, but experience has shown that the original fears were largely without foundation. By this is meant that thus far all of the children upon whom an operation has been performed have withstood anesthetization, the opening of the pleural cavity, and the temporary occlusion of one of the pulmonary arteries, and have not died during the operative procedure itself. Some subsequent events not so encouraging will be commented upon later. Furthermore, there has been no instance in which the subclavian artery has been used when there has been the slightest anxiety about the competency of the collateral circulation to the arm. Unfortunately the same statement cannot be made in regard to the cerebral circulation in all of the patients in whom the innominate artery has been divided and used for the anastomosis. This subject will be considered later in greater detail.

The selection of patients who are suitable candidates for the operation has been performed by Dr. Taussig and her associates. I should like here to acknowledge the important part which Dr. Taussig has had in all of this work. She is Director of the Cardiac Clinic in The Harriett Lane Home for Children in The Johns Hopkins Hospital and is an out-



standing authority on congenital heart disease. Many points, particularly those dealing with diagnosis, which are mentioned only briefly in this lecture, will be considered in detail by Dr. Taussig in her forthcoming book. The two outstanding diagnostic features, both of which should be present if the operation is to be performed, are (1) roentgenographic evidence that the pulmonary artery is small in size, and (2) clinical and roentgenographic evidence of absence of congestion in the lung fields. The important finding in the roentgenogram is the absence of fullness of the normal pulmonary conus. The shadow at the base of the heart to the left of the sternum is concave and not convex, the pulmonary window appears abnormally clear in the left anterior oblique position.

The studies on patients have included determinations of the oxygen content and capacity and percentage saturation of the arterial blood, the red blood cell count, the hemoglobin content, and the hematocrit reading. Patients with inadequate blood flow to the lungs do not necessarily have polycythemia but this was usually observed. The oxygen content of the arterial blood of most of the patients was lower than normal, the oxygen capacity was increased, and hence the arterial saturation was greatly reduced. Although some of the patients were cooperative and quiet at the time of the arterial puncture, most of them were crying and some were struggling. Some of the values for oxygen content would undoubtedly have been higher had the children been under basal conditions. If the arterial saturation was high in a patient with a history of poor tolerance of exertion, the effect of exercise on the saturation was determined in an effort to assess the need for operation. The findings in one such patient were as follows:

This patient was an intelligent and cooperative boy eight years of age. The control figures showed a red blood cell count of 4.7 million, a hematocrit reading of 40.5, an oxygen content of arterial blood of 18.1 volumes per cent, a capacity of 20.5 volumes per cent, and saturation of 88.2 per cent. Because of the history of intolerance of exercise it was decided to repeat the studies after the patient had climbed a few steps. After walking up only six steps, the patient refused to do more and tried to assume the usual squatting position. A sample of arterial blood taken at this time showed an oxygen content of 7.9 volumes per cent and an oxygen saturation of only 36.8 per cent. Operation was decided upon and performed, the innominate artery being anastomosed to the pulmonary artery. Slightly less than three weeks after operation the studies were repeated. The arterial saturation had risen only slightly, that is, from 88.2 per cent preoperatively to 89.7 per cent postoperatively. On the other hand, approximately twice as much exercise as the patient took before operation caused no apparent dyspnea or cyanosis and practically no change in the oxygen saturation, the postoperative figure being 88.2 per cent saturation whereas the preoperative one was 36.8 per cent. This patient returned for observational purposes on November 2, 1945, three months after

the operation. The resting oxygen saturation of arterial blood at this time was 89.2 per cent. The patient then climbed 40 steps without evidence of shortness of breath or cyanosis. A sample of arterial blood taken immediately after the exercise showed an oxygen saturation of 88.6 per cent.

The effect of exercise on the oxygen saturation varies greatly from patient to patient. It is particularly important to study the effect of exercise in patients who are quiet at the time of the control determinations and who have a relatively high resting saturation because the figures may influence not only the decision as to the necessity for operation but also may be the deciding factor in the choice of the artery which is used for the anastomosis.

Another factor which enters into the decision as to operation is the age of the patient. It is more difficult to be certain of the correct diagnosis in infants, and furthermore it is believed that they withstand the operative procedure less well than do children of the group from two to ten years of age. The youngest patient upon whom the operation has been performed was eight months and the oldest 21 years of age. Both of these patients survived the operation and are improved. At the present time it appears that children under 18 months of age should not be operated upon unless it is thought that the chances of survival to an older age are poor. A possible operative procedure that may be perfected for use in small infants will be mentioned later.

If the studies show that an operation is indicated, the patient is given penicillin for one or more days preoperatively. Neither dicumarol nor heparin is given before operation. Cyclopropane with a high concentration of oxygen was used as the anesthetic agent in most cases. In a few of the operations ether with a high concentration of oxygen was used and in others a combination of cyclopropane and ether\*. After the patient was anesthetized and before the operation was begun, usually a sample of arterial blood was withdrawn. A comparison of the results of the analyses with the control preoperative figures shows that there was an elevation in the oxygen saturation of the arterial blood in all except a few of the patients. This rise ranged from a minimal one to an increase of five times the saturation in the control period. Since many of the children were crying and struggling at the time of the control studies, it is not known whether the elevation in oxygen saturation during anesthesia was due to the fact that the patients were anesthetized

\* The anesthetic agent was chosen and administered by Dr. Lamont or Dr. Harmel of the Anesthesia Department. It is a proof of their skill that there have been no deaths during the operation on the 55 patients.

and hence quiet or to the inhalation of a high concentration of oxygen. It is probably a combination of the two factors. Most of the patients who were quiet at the time of the control studies did show an elevation of oxygen saturation when given the anesthetic agent and oxygen.

The major details of the operative procedure are contained in the previous report by Blalock and Taussig.<sup>22</sup> Adequate exposure is afforded by an anterior incision through the third interspace. There has been some alteration in our conception of the side of the chest on which the operation should be performed. Providing the position of the aorta is normal, it was our earlier idea that the approach should be made on the left if one wishes to use an artery the size of the subclavian artery and that the incision should be on the right if the use of a larger vessel such as the innominate artery is indicated. No doubt you will recall that normally the innominate artery is the first major vessel arising from the arch of the aorta and that it divides into the right common carotid and the right subclavian arteries. The left common carotid artery and the left subclavian artery normally arise separately from the aorta. When the right subclavian artery is used for the anastomosis, experience has shown that the angle of the transposed vessel at its point of origin is less acute than that seen when the left subclavian artery is employed. In other words, the lumen of the vessel appears to be less constricted by the transposed position when the right subclavian is used. For this reason it is advisable usually to make the approach on the right side. This generally allows one to choose either the innominate artery or the right subclavian artery. The preoperative studies will have given a good indication as to the size of the artery that is required. Sometimes, however, the size of the subclavian artery may be smaller or larger than was anticipated and the choice of artery may have to be altered. Furthermore, the innominate artery or the subclavian artery may be shorter than usual and it may be necessary to use the longer vessel regardless of the preoperative choice. The fact remains that the incision on the right side usually allows one to choose either the subclavian or the innominate artery according to the incapacity and the degree of arterial oxygen unsaturation of the patient. It is obvious that the greater the incapacity, the larger the vessel which is needed since the object of the procedure is to shunt blood to the lungs. In infants and small children in whom an operation is urgently needed it is generally advisable to use the innominate artery.

There is another point about the choice of artery which should be mentioned. The occurrence of a right rather than the normal left aortic arch is not rare in patients with congenital cardiovascular malformations which cause cyanosis. Bedford and Parkinson<sup>23</sup> have demonstrated that the determination of the course of the aorta is not difficult if its relationship to the esophagus is delineated under the fluoroscope as a barium mixture is swallowed. The importance of this observation rests on the fact that when the aorta descends on the right, the innominate artery is directed to the left and has to be approached through the left side of the chest. There have been 16 such patients in this series and in all the condition has been diagnosed correctly by Dr. Taussig before operation.

There are many other types of variations in the arteries which arise from the arch of the aorta. For example, both carotids and both subclavians may arise as four separate vessels, no innominate artery being present. In another variation the innominate artery gives rise to both common carotid arteries as well as to the right subclavian artery. Despite the many variations, it has been possible in every case thus far to find a systemic artery which was suitable for anastomosis to a pulmonary artery. There have been two patients, however, in whom a satisfactory anastomosis was not performed because of a variation in the right pulmonary artery. In the first of these the right pulmonary artery divided shortly after its origin and the small branch to the right upper lobe was mistaken for the main artery. This branch was too small for a satisfactory anastomosis. The proximal end of the subclavian artery was anastomosed to the distal end of the branch to the upper lobe, but the size of the subclavian was several times that of the pulmonary vessel. This patient died, and examination of the specimen indicated that the usual end to side anastomosis could not have been performed. Probably the procedure should have consisted of division of the main right pulmonary artery and the anastomosis of its distal end to the end of the innominate artery. In the second patient the right pulmonary artery was not found at the time of operation and it was only after considerable difficulty that it was located at autopsy. The artery was small and was lying inferior and posterior to the superior pulmonary vein.

The pressure in the right or left pulmonary artery was determined at the time of operation in a number of patients by puncturing the artery with a needle which was connected with a water manometer. The pressure in most of the patients was approximately 175 mm. of

water That this procedure should probably be a routine one is suggested by the following experience

In one of the patients the pressure was 310 mm of water In this patient the heart was rotated towards the right, the azigos vein was several times the normal size, and the pulsations of the pulmonary artery were much more vigorous than normal Despite the unusually high pressure in the pulmonary artery, the end of the innominate artery was anastomosed to the side of the right pulmonary artery Following operation the cyanosis did not disappear, the liver became enlarged, fluid accumulated in the pleural and peritoneal cavities, and death occurred on the 24th postoperative day At autopsy a single ventricle was found from which arose both the aorta and the pulmonary artery, and there was little if any pulmonary stenosis The preoperative oxygen saturation of 59 per cent and the red cell count of 10 million were apparently due to the complete absence of a ventricular septum It is obvious that the anastomosis should not have been performed, and the high pressure in the pulmonary artery should probably have furnished the clue as to the true nature of the condition

I shall continue with a description of the operative procedure After the systemic vessel has been chosen and prepared and the pulmonary artery has been freed from the surrounding structures, usually the end to side anastomosis is performed The right or left pulmonary artery is occluded proximally with a mechanical device Distal occlusion of the vessel is produced by making slight traction on braided silk which is placed around the individual branches of the pulmonary artery This plan as contrasted with the use of a bull dog clamp leaves a greater length of the artery free for the anastomosis A transverse opening is then made in the pulmonary artery midway between the proximal and distal points of occlusion By the use of 00000 Deknatel sutures on curved atraumatic needles an anastomosis is performed between the end of the systemic artery and the side of the pulmonary artery The continuous everting (out, in and over) suture is interrupted at least four times in order not to constrict the lumen too greatly The procedure is not particularly difficult if the arteries are of normal length and if the respiratory movements are not vigorous The operation has been described in greater detail in a previous publication<sup>22</sup>

The cyanosis usually increases during the period while one of the pulmonary arteries is being occluded Following the completion of the anastomosis and the removal of the constricting devices, the color of the patient improves immediately Usually a distinct thrill can be felt in the pulmonary artery and even in the lung tissue itself The thrill may be minimal or absent in infants

Before I leave the subject of technical procedures there are several additional points which might be mentioned As indicated previously, it is our impression that the union of the end of the systemic artery to the

side of one of the pulmonary arteries is the procedure of choice since this type of anastomosis allows the blood to pass to both lungs. There are certain circumstances, however, in which it may be advisable to divide one of the pulmonary arteries and to anastomose the end of this vessel to the end of the systemic artery. This means, of course, that all of the shunted blood passes to one lung and that the blood which passes through the stenosed pulmonary artery goes to the opposite lung. This type of anastomosis can be performed more quickly and easily and with less traction on the mediastinal structures than the one usually employed. It is possible that this method should be used more often, particularly in children. It was used in the following case as well as in three additional ones. The four patients survived the operation and are improved.

A child of slightly less than two years of age had an oxygen content of arterial blood of 3.5 volumes per cent, a capacity of 15.0 volumes per cent, an arterial saturation of 23.3 per cent, and a normal red blood cell count and hematocrit reading. The condition was considered critical and operation was advised. After anesthesia was induced by the use of cyclopropane, the arterial blood pressure fell to 50/30 mm Hg. An incision was made on the right side of the chest and the axillary vein was doubly ligated and divided. At this time the pulsations of the heart were very weak and barely visible. One half cubic centimeter of coramine was injected into the superior vena cava, and the pulsations of the heart became strong again. The right pulmonary artery was being freed of the surrounding tissues when it was noted again that the action of the heart was poor. Coramine was injected, the pulsations of the heart improved, and it was decided that the operation should be terminated. The child's condition was unchanged after this exploration and a second operation was performed 12 days later. The previous incision was reopened. The innominate artery was shorter than usual, the subclavian artery was larger than usual, and it was decided to use this latter vessel for the anastomosis. When traction was made on the right pulmonary artery, the pulsations of the heart practically ceased. Coramine was injected and the condition improved. In order to avoid unnecessary traction and in order to reduce the operating time, the right pulmonary artery was ligated and divided and its distal end was anastomosed to the end of the subclavian artery. The action of the heart became very weak on two occasions while this was being done, but it responded favorably when coramine was injected. It is doubtful whether the procedure could have been completed successfully if an end to side anastomosis had been performed. The child showed a dramatic improvement. Twelve days following the second operation the arterial oxygen content was 10.1 volumes per cent, the arterial capacity was 16.3 volumes per cent, and the arterial saturation was 62 per cent as compared with the preoperative figure of 23 per cent.

Another point in operative technique which deserves brief mention is the possibility of connecting the lumen of the aorta with that of the main pulmonary artery without the use of sutures. The first portions of the medial walls of the aorta and the pulmonary artery are intimately adherent to each other largely because they are enclosed in a tube of serous pericardium common to the two arteries. In the dog it is possible

to connect the two vessels by a stab incision. There are, however, several points in technique which have not been mastered. There is danger of piercing the opposite wall of the aorta, there is no accurate gauge as to the size of the opening, and the fistula, even though moderate in size, may close spontaneously. This problem is still in the experimental stage. It is to be hoped that some such method can be perfected because it may be necessary to use the major blood vessels and to work with considerable speed if newborn infants with pulmonary stenosis or atresia are to be operated upon successfully.

Treatment both during and after the operation will be considered briefly. As a routine procedure a needle is placed in a vein of the ankle before the operation is begun and a very slow infusion of normal saline solution is given. If an abnormally large quantity of blood is lost, plasma is administered. If the patient has pronounced polycythemia and if the loss of blood during the operation is minimal, whole blood equal to approximately one per cent of the body weight is removed at the conclusion of the operation. As soon as the patient is returned to his room he is placed in an oxygen tent. The administration of penicillin which had been begun preoperatively is continued for about two weeks. It is of interest that none of the patients had a post-operative infection. Until recently the administration of dicumarol was begun 24 hours after operation in most cases and was continued for about two weeks. Its use was discontinued when a patient died because of intrapulmonary bleeding. Heparin is not given unless evidence of cerebral thrombosis appears.

The postoperative course of the patients was variable. Those patients who were benefited by the operation showed an early improvement. As soon as the operation was completed, the mucous membranes showed much less cyanosis. It required, however, a longer time for the disappearance of cyanosis of the fingers and toes. The fact that the color of the mucous membranes changes almost immediately following the operation is further evidence of the importance of the volume of the pulmonary blood flow in these patients in the production of cyanosis. In this early postoperative period there has been little alteration in the red blood cell count, the hemoglobin content, and the hematocrit reading even though moderate blood loss has occurred. The one important factor which has been altered is the volume of blood which reaches the lungs for aeration.

I stated previously that there has been no concern about the circulation of the arm, the subclavian artery of which was divided and used for the anastomosis. Sympathetic nerve block was not used in any of these cases. The arm of the operated side was slightly cooler than the opposite one for varying periods of time. Motion and sensation were little if at all affected. The radial pulse has reappeared in some of the patients. Either the right or the left subclavian artery was divided and used for the anastomosis in 26 cases. In 23 additional cases the innominate artery was used and it is apparent that it was necessary to ligate the first portion of the subclavian artery in each of these. Thus, the first portion of either the right or the left subclavian artery was ligated in 49 cases, there was no evidence in any case of dangerous interference with the circulation of the arm. These 49 cases include a duplication in one patient in whom the left subclavian artery was used at the first operation and the innominate artery at the second.

There follows a brief account of the experiences of other surgeons with ligation of the first portion of one or the other of the subclavian arteries. Halsted in 1921 found that the first portion of the left subclavian artery had been ligated in 21 cases. A recent search of the literature provided the records of 13 additional cases in which the first portion of the left subclavian artery was ligated. Of the total of 34 cases, 14 were performed in the treatment of aneurysms, 19 for trauma, and one for a tumor. There were nine deaths in this series. There have been found in the literature references to 57 cases in which the first portion of the right subclavian artery was ligated. The operation was performed because of an aneurysm in 36 cases and because of trauma in 21 cases. There were 24 deaths in this series. It was not necessary to perform an amputation of the arm in any of the patients who survived ligation of the right or left subclavian artery.

I have stated previously that the innominate artery was used for the anastomosis in 23 of our patients. This fact implies, of course, that one of the common carotid arteries and a subclavian artery were ligated in each of these patients. There were seven deaths in this series. In two of the seven cases the preoperative diagnosis was in error. In two of the remaining five cases death was attributed to cerebral ischemia or thrombosis. Unfortunately an autopsy was not obtained in these two cases.



In several additional patients transient weakness of part or all of the opposite side of the body occurred after operation

A review of the literature from the time of Valentine Mott's operation in 1818 to the present lists 86 cases in which the innominate artery has been ligated. There were 48 postoperative deaths, a mortality rate of 55.8 per cent. There were six cases of complete hemiplegia with four deaths and five cases of partial hemiplegia with two deaths. Eighty of the 86 ligations of the innominate artery have been performed in the treatment of aneurysms. There were 43 postoperative deaths, a mortality of 53.7 per cent. The remaining six ligations were performed in the treatment of trauma. There were five deaths, a mortality rate of 83 per cent. Prior to the initiation of the present work the innominate artery had not been ligated for conditions other than aneurysm and trauma.

In five of our cases in addition to the twenty-three in which the innominate artery was used for the anastomosis, the common carotid artery was ligated and divided and connected to one of the pulmonary arteries. This artery was used because of an abnormality in the position of the vessels which arose from the aortic arch. There was no sustained evidence of disturbance of the cerebral circulation in these five patients.

Before summarizing the results of the operations performed thus far, I shall relate some of the details of two cases. In the 2nd case of the series the oxygen saturation of arterial blood rose from 36 per cent before the operation to 83 per cent three weeks later. Five months after operation the saturation was 87 per cent. The red blood cell count dropped from 7.7 to 5 million. The hemoglobin declined from 24 to 17.5 grams, and subsequently to 15.5 grams. In the third case of our series the oxygen saturation rose in nine days from 35.5 to 80 per cent and subsequently to 83.7 per cent. In three and a half months the red blood cell count declined from 10.1 to 5.6 million, the hemoglobin fell from 26 to 13.8 grams and the hematocrit reading changed from 81 to 38. Both of these children were incapacitated before the operation. Now they are able to walk and play and go to school. These two cases are mentioned because the follow-up period has been longer than in others who show equally striking improvement.

I shall attempt now to give the results thus far in The Johns Hopkins Hospital of the creation of an artificial ductus in the treatment of

pulmonary stenosis Up to November 1, 1945 there were 57 operations on 55 patients All of the operations except one were performed in the nine months' period from February third to November first An anastomosis between a systemic artery and one of the two pulmonary arteries was not performed in three cases In two of these there was an anatomical abnormality of the pulmonary artery and in the third there was thought to be an error in diagnosis The first two patients have died since the operation The condition of the third patient is unchanged In the remaining fifty-two patients, forty are improved, two have shown little change, and ten have died

The deaths will be considered first The preoperative diagnosis of the tetralogy of Fallot was proved by autopsy to be in error in two of the ten cases One of these patients had a transposition of the great vessels and the other had a single ventricle without pulmonary stenosis Theoretically these patients would not have been helped by operation even if they had survived An autopsy was performed on six of the remaining eight patients and the preoperative diagnosis of the tetralogy of Fallot was confirmed One could not be certain of the cause of death in most of these patients Except for the cardiovascular defects the pathological alterations were minimal None of the patients had an empyema or mediastinitis As far as could be ascertained, bleeding from the arterial anastomosis did not occur in any of the patients Two of the deaths were probably due to cerebral ischemia or thrombosis but a postmortem examination of this region was not allowed One of the patients who had been doing very satisfactorily succumbed suddenly on the fifth postoperative day from pulmonary hemorrhage The anastomosis was intact, and it is believed that the bleeding was due to the dicumarol that had been given In one case bilateral pneumothorax developed following the first operation and unilateral tension pneumothorax following the second operation A congenital abnormality of the lungs was suspected but an examination was not allowed If the two cases are excluded in which it was shown at autopsy that the diagnosis was incorrect, there were eight deaths in the remaining fifty patients in whom the anastomosis was performed, a mortality of 16 per cent

It has been stated that two of the patients who survived showed little if any improvement In one of these, a boy of 15, the intima of the subclavian artery was injured by too vigorous application of the

instrument which was used in occluding it. A thrill could not be felt at the end of the operation and a murmur could not be heard later. A second operation on the right side is to be advised in the future. In the second patient a large right pulmonary artery was found at operation and the pulsations were vigorous. The anastomosis was performed even though it was thought at the time that the diagnosis was in error. It has now been seven months since the operation was performed. The parents state that the child is moderately improved. It is our impression that the improvement, if any, as a result of the operation is minimal.

The improvement in the remaining 40 patients is definite. The condition of most of the children has been altered from almost total invalidism to apparent if not real normality. Most of them show no cyanosis, even with moderate effort, and the clubbing of the fingers and toes has disappeared or is diminishing. Some children who had never walked before operation are now able to walk. The average oxygen saturation of arterial blood of these patients prior to operation was 49 per cent and the average saturation when determined two to three weeks after operation was 76 per cent, an average increase of 53 per cent of the control level. It was stated previously that many of the children were not under basal conditions at the time of the arterial punctures and that otherwise probably both the preoperative and postoperative figures would be higher. Although the oxygen saturation of the arterial blood rises greatly, it does not reach the normal value of 95 to 98 per cent saturation. This finding is to be anticipated because in every instance of the tetralogy of Fallot there is an inter-ventricular septal defect and varying degrees of dextroposition of the aorta with overriding of the septum, and hence the aorta always receives some poorly oxygenated blood from the right ventricle. It has been possible, however, in most of these patients to cause an elevation of the arterial oxygen saturation to the point where the stimulus for the development of polycythemia has largely disappeared or has been abolished. The decline in the oxygen capacity has been greater in most patients than has the elevation in the arterial oxygen content. The objective in the performance of the operation is the establishment of a channel by which an adequate quantity of blood can reach the lungs. This pulmonary flow should be adequate to permit growth and the performance of exercise, and to cause the disappearance of polycythemia and cyanosis. It should not be excessive because this will place

an undue strain on the heart. There has been only one patient thus far in whom cardiac enlargement since operation has been great enough to cause concern. Dr. Taussig has found that a number of the patients have shown a slight increase in the size of the heart in the early post-operative period, but this enlargement has not been progressive. Streptococcus viridans infection has not developed in any of the patients.

It is important to emphasize the point that the operation is not of value to all patients with persistent cyanosis.<sup>22</sup> It is indicated only in malformations in which the primary difficulty is lack of adequate circulation to the lungs. More specifically, the types of abnormalities which should be benefited by the operation are the tetralogy of Fallot, pulmonary atresia with or without dextroposition of the aorta and with or without defective development of the right ventricle, truncus arteriosus with bronchial arteries, and a single ventricle with a rudimentary outlet chamber in which the pulmonary artery is diminutive in size. The operation is not indicated in cases of complete transposition of the great vessels or in the so-called "tetralogy of Fallot of the Eisenmenger type" and probably not in aortic atresia.

The purpose of this lecture has been to discuss certain congenital cardiovascular defects in which treatment by surgical means is proving effective. The incompleteness of knowledge is excusable in view of the only recent application of these methods. It is to be hoped that the advances recorded thus far will serve as an added stimulus to further studies on cardiorespiratory physiology, including the problem of chronic anoxia, and to the development of additional and improved methods for the treatment of cardiovascular defects.

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# THE TREATMENT OF ANEURYSMS AND ARTERIOVENOUS FISTULAS\*†

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ACCOUNTS of injury to blood vessels in warfare have been recorded since the beginning of history, and the attention of surgeons has of necessity been primarily directed towards their treatment because of their often fatal nature. The arrest of hemorrhage and the preservation of an adequate arterial supply to the extremities have been, in fact, the main concern of military surgeons since the dawn of recorded medical history, and numerous papers concerning vascular injuries have appeared in medical literature following every war. The number of such injuries has increased steadily, probably due to the introduction of higher velocity projectiles of smaller caliber. In addition to the ordinary wounds caused by machine guns, rifle bullets and shrapnel, a great many multiple injuries were produced by the fragmentation of land mines, grenades and aerial bombs. These latter may produce as many as two hundred small individual wounds scattered over the body without causing death, thus increasing the chance of trauma to blood vessels. It was, therefore, to be expected that the sequelae of these injuries would be encountered more numerously than ever before. Moreover, improved methods in the control of hemorrhage, shock, and infection have preserved more individuals for subsequent observation and study.

In order to bring about more highly specialized treatment of certain surgical conditions, The Surgeon General established centers for their treatment. In view of the fact that Ashford General Hospital was designated the first center for vascular surgery, a larger proportion of this type of injury has been seen at that institution.

For descriptive purposes, vascular injuries as the result of war wounds may be divided as follows:

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- 1 Partial severance of a vessel producing a false aneurysm or arteriovenous fistula

- 2 Those in which the blood vessel is completely severed or in which vasospasm exists to such an extent as to so impoverish the blood supply that death of the part or useless fibrosis results

- 3 Activation of previously existing blood vessel disorders or tumors, such as congenital nevi and pre-existing vascular injuries

This report is concerned only with the operative treatment of traumatic aneurysms and arteriovenous fistulas, approximately 450 of which have been treated at the Vascular Surgery Center at Ashford General Hospital in the past two and one-half years

All of these aneurysms and fistulas, with rare exceptions, were the result of battle wounds and in all a considerable time ranging from weeks to months had elapsed between the time of injury and their reception at the hospital. It is not the purpose of this paper to discuss in detail the pathogenesis and diagnosis of these lesions. When an artery is completely divided, both ends retract and although hemorrhage may be severe at first it may stop spontaneously, or with the application of pressure. On the other hand, it may require ligation or some attempt at repair. However, if a vessel is only partially severed, the wound tends to enlarge in the long axis of the vessel due to retraction, and hemorrhage is apt to be profuse. If the wound in the soft tissues overlying the vessel is large, hemorrhage of course will be external and will probably require immediate control. If, however, the wound is small, the overlapping of the various muscle, fascial and skin planes may prevent the escape of blood externally. This results in the formation of a hematoma which is likely to become a false aneurysm. Moreover, in instances with a small external wound, if the vein is injured at the same time, an arteriovenous fistula may result, the artery and vein communicating directly or through the medium of a false sac. In either case it is well to remember that some blood continues to flow through the distal portion of the artery, thus nourishing the part beyond, and that collaterals develop rapidly. Therefore, immediate operation is always contraindicated unless necessitated by hemorrhage or rapid enlargement of an aneurysmal sac which compresses the vessels of the collateral circulation.

Openings in blood vessels produced by small missiles may for a time produce no symptoms. For this reason, these lesions are frequently over-

looked, particularly if more striking or extensive injuries are present. The value of auscultation as a means of determining their presence cannot be too strongly stressed. In the presence of a large number of casualties and under battle conditions, a diagnosis, although incomplete or even incorrect, may be carried by a wounded soldier for some time. This does not imply that proper treatment has not been given, but it does entail on those who are working in hospitals distant from the battlefield the necessity of careful examination uninfluenced by any previous diagnosis. Moreover, it is a well known fact that a vascular lesion may develop slowly to the point of recognition. For example, an arteriovenous fistula may not show characteristic signs until edema and hemorrhage have subsided. It is well to remember that blood vessels are usually accompanied by nerves and that nerve lesions which are so striking in their immediate manifestations may mask or cause to be overlooked accompanying blood vessel trauma. Inconspicuous wounds may likewise involve blood vessels and aneurysms resulting from such wounds are frequently overlooked through failure of the examining surgeon to suspect their presence or because his attention has been drawn elsewhere to a seemingly more important lesion. Aneurysms of various types will be overlooked unless every wound is carefully examined, particularly by auscultation.

The differentiation of a false arterial aneurysm, and an arteriovenous fistula is extremely important, since the sequelae, the general and local effects, as well as the treatment of the two conditions differ greatly. The differential diagnosis is not always easy, but as a rule the arteriovenous communication is characterized by a continuous vibratory thrill and a loud, rough, *continuous* murmur with systolic intensification, whereas in the false aneurysm, there is a distinct pause between the systolic and diastolic phases and often the murmur is heard only in systole. In an arteriovenous communication, the murmur is usually transmitted for some distance on either side along the course of the vessels, whereas in an aneurysm confined to an artery, the murmur is rarely heard beyond the confines of the dilatation. In the case of a fistula, the swelling is usually less pronounced, although some fistulas, with a false sac, may give rise to a tumor of considerable size. The dilatation of cutaneous veins in the region of the fistula, and the slowing of the pulse on temporary occlusion of the fistula are further differentiation points. In large fistulas or in those persisting over a long period of time cardiac



dilatation with subsequent heart failure is likely to follow

In the 450 instances of aneurysms and fistulas, 110 were false, traumatic, arterial aneurysms and the remainder were fistulas. Since anatomically they presented many of the same problems they will be discussed together. They were encountered in practically every named blood vessel of the body with the exception of the aorta, and many have presented varied problems of approach and treatment.

The arterial aneurysms have in general been treated by the Matas principle of intrasaccular suture or by ligation and excision. In aneurysms of large size, the Matas operation was preferred but those of smaller size, particularly if accompanied by nerve injury, were treated by excision of the vascular lesion with nerve repair or neurolysis carried out at the same time.

In general, the arteriovenous fistulas have been treated by quadruple ligation and excision, although in twelve instances it has been possible to repair the fistula and preserve the continuity of the artery. The latter course is preferred, but it is usually impossible because of dense scarring, previous infection, and the usual presence of a false sac.

There have been five instances of fistula between the cavernous sinus and internal carotid artery. Two of these were cured by ligation of the common carotid artery alone. In two others it was necessary to ligate the internal carotid artery distal to the fistula since ligation of the vessels outside the skull did not effect a cure. A third was cured only after ligation of both common, both internal, and both external carotid vessels.

Cirsoid aneurysm of the scalp following trauma, usually superimposed upon a pre-existing nevus, has been treated successfully in five patients. After preliminary ligation of the external carotid vessels, a flap of the scalp containing the fistula is turned back, the incision being carried through the galea to the pericranium. The fistula with its ramifications can then be removed from the underside of the flap, particular care being taken not to buttonhole the skin.

A number of aneurysms and fistulas of the carotid vessels and their branches has been treated either by the Matas method in the case of arterial aneurysms and by quadruple ligation and excision or by repair in the case of fistulas.

There have been nine instances of fistula of the vertebral vessels. They have been by far the most difficult problem, both in diagnosis

and treatment In only two was the diagnosis definitely established before the operation, although in others it was strongly suspected In general, if the bruit could be obliterated by pressure upon the common carotid artery, the vertebral vessels were considered to be the probable seat of the lesion The approach to these vessels is difficult, either in the first, second, or third portion, because of their deep position in the neck and their passage through the transverse processes of the cervical vertebrae In any event, preliminary ligation of the artery close to its origin should be carried out If the lesion is high, that is, near the base of the skull, it is best approached by detaching the sternomastoid and levator scapulae muscles If lower in the neck, it is approached through the tissues just lateral to the carotid sheath and in any event it may be necessary to remove one or more of the transverse cervical processes in order to provide proper exposure

In the approach to the greater vessels at the base of the neck, the clavicle frequently prevents adequate exposure and control of the vessels proximal and distal to the vascular lesion The safety of an operation on those vessels depends largely upon the accuracy with which this isolation and exposure is accomplished It has long been recognized that the removal of a portion of the clavicle will greatly increase the exposure, but the problem of repair of the clavicle has led to many variations in wound closure Following subperiosteal removal of a segment, it is a common practice to replace the excised bone with some type of wire or metal fixation Deformity, non-union, and pain frequently follow such a procedure Forty-five patients have been operated upon for aneurysms and fistulas of the subclavian, axillary, carotid, and innominate vessels and their branches, in whom the clavicle has been partially removed In lesions at the base of the neck and the superior mediastinum, resection of the medial half of the clavicle together with its sternal articulation has been done The subclavian and axillary vessels have been approached by resection of only the center third of the bone *The excised segment of the clavicle was not replaced in any of these patients* There was little postoperative deformity—certainly less asymmetry than is observed when the clavicle is replaced In eighteen additional cases, it was removed without replacement for operation upon the brachial plexus and in one other a portion was resected because of painful union of a fracture with subsequent relief of pain and improvement in the function of the arm

Operations upon the common, external, and internal iliac vessels have been carried out through a retroperitoneal approach which is preferable to a transperitoneal approach since the abdominal contents are more easily displaced and are less apt to be injured. In operations upon the gluteal vessels, the common iliac artery is temporarily occluded as a preliminary step.

Aneurysms at the junction of the external iliac and femoral vessels, that is, in the neighborhood of Poupart's ligament, can usually be exposed through an incision parallel to and just above Poupart's ligament.

The best guide to the femoral vessels is the sartorius muscle which in the upper portion of the thigh lies lateral to them and in the middle and lower portion overlaps them in their course in Hunter's canal.

The upper popliteal and lower femoral vessels are reached through an incision just anterior to the sartorius muscle. With the knee flexed and externally rotated, the muscle is easily displaced posteriorly when the deep fascia is opened.

Care should be exercised in the placing of skin incisions so that they do not cross skin creases perpendicularly. This is particularly important in the popliteal and cubital spaces, where the incisions should be S or Z-shaped, so that one limb of the incision crosses the space transversely. Otherwise, contracting keloids are almost certain to form.

A near disaster from hemorrhage of the posterior tibial vessels has prompted the approach to these vessels by the removal of the upper portion of the fibula including the resection of the head of that bone where necessary. The same approach is used to reach the anterior tibial and peroneal vessels in the upper portion of their course. It is often impossible to differentiate by clinical measures which of these three vessels is involved because of their close proximity to each other. The fibula is removed subperiosteally, thus insuring continued stability of the knee joint. In no instances has the bone been replaced.

Resection of the fibula for exposure of these vessels is necessary only in their course in the upper portion of the leg. In the lower third of the leg the peroneal and posterior tibial vessels are more easily reached by an incision made along the posterior surface of the tibia on the medial side of the leg, and the anterior tibial vessels are best isolated by an incision directly over them on the anterior surface.

Wherever possible, an incision should not be made on the sole of the foot since it is invariably painful on weight-bearing. To approach

the plantar vessels, therefore, the incision is made on the medial side of the foot, the abductor hallucis muscle is detached from its origin, and the vessels with the tibial nerve are traced into the deeper structures of the foot

Operations upon the lower extremities were done almost entirely under continuous spinal anesthesia. Operations upon other parts of the body were usually done under pentothal sodium anesthesia supplemented by nitrous oxide and oxygen. There were no complications of consequence attributable to the anesthetic. Altogether, half of the operations required more than three hours and some as much as seven hours. The advantages of continuous spinal became apparent in such lengthy operations.

There were no instances of gangrene in this series. Sympathectomy and sympathetic block were rarely performed either before or after operation, although the advantages of it are thoroughly appreciated. The time interval between the origin of the wounds and operation averaged three months and was rarely less. Thus, ample time for the development of collaterals was allowed. Had operations of necessity been performed at an earlier date, no doubt sympathetic interruption would have been more frequently performed.

*Complications* There was one death in this series due to secondary hemorrhage following excision of an arteriovenous aneurysm of the subclavian vessels. The fistula was so close to the aorta that the vessels could not be transfixed with sutures, a procedure always carried out in operating upon vessels of any size. There were two instances of cerebral anemia with paralysis following operation upon the carotid vessels. One of these was transient, the other permanent. In ten patients more than one operation was necessary to effect a cure. In two of these, four operations were performed. Three patients were not cured by operation, all of them with arteriovenous fistulas of the internal carotid vessels at the base of the skull which could not be completely eradicated because of their position.

## THE HORMONAL TREATMENT OF PROSTATIC MALIGNANCY\*

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THE treatment of carcinoma of the prostate by hormones is a biological approach to a problem in clinical medicine. The results of hormonal treatment stimulate optimism for the treatment of an incurable disease. Men who have been bedridden or paralyzed for months and have suffered from dysuria, incontinence and retention of urine have been greatly benefited by castration or by the administration of synthetic hormones or both. Others who have experienced severe pain from metastatic lesions of the spine have been rendered free from pain and have been given a new lease on life, such that they are able to void urine comfortably, to get out of bed, to walk about naturally and, in many instances, to return to their former vocations. The author has several patients who have been invalided by prostatic cancer and who now, after hormonal treatment, work seven days per week in war industries. The encouraging results in many cases and the miraculous response of a few isolated cases of prostatic cancer to hormonal therapy do not necessarily signify that complete control of the neoplasm is being achieved in all cases. Due to the slow growth of prostatic cancer a long period of observations, with a rigid analysis of the reports, seems necessary for evaluation of the estrogenic response.

Lest our optimism becloud our horizon of commonsense and perjure our scientific consideration of biological facts, we will do well to consider ourselves still on the avenue of research in the field of prostatic cancer. We have some of the answers but not all of them, for there exist complex issues concerning carcinogenic elements in the gonads and allied internal secretions in old age. Longevity invites the development of cancer of the prostate, longevity not only diminishes hormonal ac-

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tivity but produces an imbalance of internal secretions. Nature, it seems, has planned that our demise be occasioned by cancer of the prostate. In our defense to cancer growth, we are adopting a belligerent attitude towards nature and are devising a plan of combat which will not only control the growth of cancer of the prostate but will prevent its development. We are employing the biologist to aid us in preventing normal epithelial cells from changing into cancer cells. We are asking the biochemist to give us measures whereby we may maintain the secretion of our hormones and preserve a balance of the secretions of the internal glands in old age in order that we may live just a few more years.

The span of life has advanced from 47 to 64.2 years in the last three decades. Cancer of the prostate is actually on the increase. A few cases are seen in the 40's. Fourteen per cent of all males past 44 years have cancer of the prostate. As we reach the 70-year mark it is estimated that one man in seven has cancer of the prostate. The average age of the prostatic cancer patient is 67.8 years. This does not signify that all of those having cancer of the prostate at this age will die from the disease. At present there is a strong feeling that cancer of the prostate is related to a carcinogenic agent in the gonads. The indomitable will of men to live longer and more comfortably urges the scientist to deploy his investigative pursuits into the realms of the relationship of cancer of the prostate to hormones and requests that the answer be found either by eradicating the gonads of the male or by neutralizing the male hormones by the administration of the hormones obtained from the gonads of the opposite sex.

There have been two eras of popularity for treating prostatic tumors by hormonal means. We are now in the midst of the second era. The first period began in 1891 and continued for about 10 years. The treatment of prostatic tumors by castration was not wholly accidental but based upon a certain number of clinical observations and animal experimental evidence. More than a hundred years ago in 1836 Leroy d'Etiolles<sup>1</sup> and Civiale<sup>2</sup> noted that patients who had orchidectomies in conjunction with the repair of double inguinal herniae subsequently developed an atrophy of the prostatic gland. Gruber<sup>3</sup> in 1859, Pelikan<sup>4</sup> in 1875 and Griffiths<sup>5</sup> in 1889 reported complete degeneration of the prostatic gland after castration in the dog and cat. White<sup>6</sup> in 1891 was the first to note the histological changes in the prostate after hormonal therapy. He demonstrated that after castration in the dog the glandular

and then the muscular elements of the prostate atrophied and suggested that castration be done in the human for benign prostatic lesions. It was during the next few years that many men lost their testicles for prostatic disease without differentiation as to a benign or malignant lesion. Cabot<sup>7</sup> in 1896 was able to report 203 cases of prostatic enlargement treated by castration, 83.6 per cent of which showed improvement, 6 per cent without much benefit and 9.8 per cent failures. It was at this time that the treatment of cancer of the breast by ovariectomy was instituted, but the idea of treating cancer of the prostate in an analogous manner was not apparent. At the turn of the century castration therapy for prostatic disease was looked upon with great disfavor by both the patient and his wife with the result that surgical treatment superseded castration therapy.

There was an intervening period of 35 years before the second era of hormonal therapy was initiated. Strohm<sup>8</sup> in 1935 made two discoveries: (1) that female sex hormones were a "boon" to prostatic cancer, and (2) that the injection of placental blood caused relief of pain at the site of bone metastases. The next year Counseller<sup>9</sup> stated that by applying x-ray therapy to the testes in sterilizing doses pain in prostatic cancer patients disappeared. In 1940, Kahle and Maltry<sup>10</sup> castrated 14 patients who had benign prostatic hypertrophy with some improvement of their symptoms and reduction in the height of the prostatic gland epithelium. Kutscher and Wolbergs<sup>11</sup> in 1935 demonstrated that the prostatic gland contained an enzyme, phosphatase. In 1936, the Gutmans and Sproul<sup>12</sup> found phosphatase in bones containing metastatic prostatic cancer and that the blood contained both alkaline and acid phosphatase. Two years later, in analyzing prostatic glands at various age groups, they demonstrated very little of the phosphatase in the infant prostate and more in the young adult prostate. Gomori<sup>13</sup> showed that only the acid phosphatase was present in the epithelial cells of the normal adult prostatic gland. It has further been shown that the malignant prostate contains more acid phosphatase than the normal gland.

Huggins,<sup>14</sup> appreciating the work of these authors, demonstrated that he could diminish the amount of serum acid phosphatase in the prostatic secretion of the dog by castration and that he could also diminish it by giving stilbestrol without castration and that the experiment was reversible. As long as the prostatic cancer is limited to the prostatic capsule there is little if any elevation of the blood serum acid

phosphatase The prostatic cancer cells liberate the serum acid phosphatase when metastatically placed and especially when in bony tissue No other cancers produce any appreciable elevation of serum acid phosphatase so that it is considered of diagnostic value for bony cancerous lesions metastatic from the prostate

There is general agreement among observers that an elevation of serum acid phosphatase determined by either the Bodansky or King-Armstrong methods is significant The type of cancer influences the acid phosphatase reading to some degree The large tumor formed by the adenocarcinoma gives a higher reading than the small tumor formed by the scirrhus type The readings run sometimes up into the hundreds of units per 100 cc of blood and a few into the thousands There is considerable variation in the readings and some doubt is now being raised as to the exact value of these observations When the serum acid phosphatase is elevated it can be reduced either by castration or by the administration of estrogen On the contrary, it can be elevated again by the administration of androgens, and the prostatic tumor takes on a more active growth In about 60 per cent of patients with an elevated serum acid phosphatase, according to Herger and Sauer,<sup>15</sup> castration produces a dramatic drop of 59.6 per cent in 24 to 48 hours and 75 per cent in 7 days Most observers are in agreement with these figures Stilbestrol alone produces a less dramatic drop but reaches 63.8 per cent drop in 7 days If castration be done and stilbestrol be administered at the same time, there is very little change in the rapidity in the drop of the serum acid phosphatase in the first 48 hours Twenty per cent of patients who by clinical and x-ray examinations show metastatic lesions do not have elevated serum acid phosphatase readings or have marginal readings There is also a group of about 20 per cent of patients who do not show a drop in serum acid phosphatase after either castration or stilbestrol administration These latter fail to develop any clinical improvement and run a progressive downhill course as if no attempt at hormonal treatment had been instituted Those who respond favorably and have a return to normal serum acid phosphatase levels maintain it for varying lengths of time A very few after three months begin to show again an elevation of serum acid phosphatase and also a re-occurrence of clinical signs of the tumor and a progressive course of the disease, although most of the patients in the author's series who have died have done so without elevation of the serum acid phosphatase



The temporary period of return to normal of the serum acid phosphatase is explained either by diminished production of the enzyme or by greater difficulty of its entry into the circulation. Neither castration nor the administration of stilbestrol will cause the serum acid phosphatase to enter the circulation. An elevated serum acid phosphatase means a metastatic lesion from prostatic cancer and can be relied upon as a test for neoplastic activity originating in the prostatic gland, although the reverse is not true.

The favorable clinical response to hormonal therapy is manifested by loss of pain, improvement in general condition, gain in weight, improvement in urinations, cessation of hematuria, reduction of edema of legs, when present, regression of the primary lesion and, in a few instances, the regression of the metastatic lesions. The most dramatic response is the disappearance of back pain, which has been so resistant to heat, drugs and irradiation therapy. After castration, unremitting pain disappears within 24 to 72 hours. Usually 50 per cent of the pain is gone in 24 hours, slight pain remains at the 48-hour period and on the third day patients admit that they are free from pain and no longer need anodynes. With the use of stilbestrol the pain disappears more slowly but is usually entirely absent at the end of 7 to 10 days, depending somewhat on the amount of stilbestrol administered. Some are described as improved, and there remains about 20 per cent who are not relieved. If castration does not relieve the pain, stilbestrol will not, if used as a subsequent therapeutic measure. There may be rare exceptions to this rule, but we have not encountered them.

General improvement in some degree occurs in 80 per cent of the patients after subsidence of the pain. Anorexia is replaced by a desire to eat and the ingestion of most foods. Sixty-six per cent gain from 10 to 60 lbs in weight. Some bedridden patients walk for the first time in months and are again desirous to return to their jobs. About 20 per cent either show no change in weight or continue to lose weight and run the usual clinical course of individuals suffering from a fatal malignant disease. Other patients apparently do well for 3 to 22 months and then begin to lose weight and die, but they never become really emaciated. This group has been dubbed "delayed failures" by Reed Nesbit<sup>16</sup> of Ann Arbor. The longer we follow our cases the more we are compelled to transfer our apparent controlled lesion cases into the group of delayed failures. Eventually all may fall in that group. This is a

pessimistic statement, but we must be very guarded in our observations because many of the present reports are premature. Prostatic cancer is a slow-growing malignancy, and final results can not be determined until the patient dies.

The effect of hormonal therapy upon urinations is somewhat obscured by the numerous palliative measures for relief of urinary obstruction, such as suprapubic drainage, partial prostatectomy by suprapubic and perineal routes and transurethral resections. We can say that most of those who had a small prostatic tumor treated by suprapubic drainage alone with subsequent hormonal treatment have dispensed with their suprapubic tubes, with the result that their wounds have healed and they have resumed normal urinations for many months, but most of them have eventually developed obstruction again. There are a few reports of a small group of patients who did not have retention of urine and who have not been treated surgically. We have but few of these cases in which our only surgical procedure was a perineal biopsy. The urinary frequency begins to lessen in about 10 days in those cases who do not have retention and gradually improves up to 6 or 8 weeks. Those who passed bloody urine ceased bleeding in 8 to 10 days. Herbst<sup>17</sup> reports that one case showed a change from severe dribble and hourly urination to four to six hourly urinations twenty-four hours after intramuscular injection of estradiol dipropionate. Such a miraculous response reminds one of a report which came from Chicago after the institution of hormonal treatment for undescended testicle, in which there appeared the statement that 20 minutes after the injection of the hormone the undescended gonad was found lying in its normal position in the scrotum. It seems hardly fair to ascribe such rapid action as wholly due to the effect of the hormone. We have not had the good fortune to obtain such spectacular reactions. Reports from Buffalo Cancer Clinic and elsewhere would indicate that 42 to 86 per cent are temporarily relieved of urinary obstruction by hormonal treatment alone. This factor is variable, and diversity of opinion is probably explained on the ground of the observer's point of view. Herger<sup>18</sup> states that in the non-operated cases treated with hormones 58.6 per cent had no relief of urinary symptoms at the end of one year.

We feel keenly that when there is obstruction with residual urine the obstructive factor should be immediately removed by surgery. This allows a better renal function and, if the urinary tract is infected an-

opportunity to banish this serious part of the problem. There is no agreement as to what surgical procedure should be utilized. Reports are anything but uniform. Some urologists treat all by transurethral resection. We have had some excellent temporary symptomatic results by this procedure, but some patients are made worse, suffer from an extensive ulceration of the neck and base of the bladder and are very uncomfortable. In our experience, the patients treated by conservative perineal excision have responded the best. Belt<sup>19</sup> of San Francisco is of this same opinion. Basically we all should recall to mind that the mucous membrane of the urethra and bladder acts as a barrier to invasion and extension of a malignant process. Why remove the natural barrier by transurethral resection? If there is any time in life at which we need to utilize the natural barriers to cancer extension it is at this time. When the obstructive tissue is removed via the perineal route much of the mucous membrane of the posterior urethra can be conserved, thus utilizing this natural hurdle to cancer growth and at the same time removing much of the primary growth.

During the year 1944 an attempt was made by Vallett,<sup>20</sup> Colston<sup>21</sup> and Scott<sup>22</sup> to make an inoperable cancer of the prostate an operable one by preliminary castration and estrogenic administration. Vallett first removed the obstruction by transurethral resection, two months later performed a castration, and 70 days later, a radical perineal prostatectomy. The patient remained clinically free from cancer but died one year later of cardiovascular disease. An autopsy was not obtained. Scott reported in January of this year a series of five cases treated by hormonal means followed by radical perineal prostatectomy. Colston believes that selected endocrine therapy is applicable to a certain number of cases preliminary to radical surgery. The idea is to be commended, but the results, of course, can not now be evaluated.

The effect of estrogenic hormones on the primary tumor is, in some cases spectacular, in other cases there is softening without appreciable regression, and, in still other cases, there is no noticeable change. The cases which respond favorably show a softening of the prostatic gland in about one month, and complete regression in 3 to 5 months in 33 per cent of cases. Herger and Sauer<sup>18</sup> believe that the majority of the complete regressions take place in the first six months, a few in nine months, and rarely in twelve months of therapy. Patients who show the greatest local change in the tumor have the greatest symptomatic relief.

There is much difference of opinion concerning the effect of estrogenic hormones on *metastatic* lesions Bumpus and Nesbit report cases in which lung metastases have disappeared following hormonal therapy Graves of Boston reports a case which, four months after treatment, showed by clinical observations regression in the size of the cervical and inguinal lymph glands and histologically disintegration of the cancer cells Dean<sup>23</sup> reports complete disappearance of a bony lesion of the femur proved by x-ray examination These authors report that the patients have also shown a favorable general response as well as a drop in serum acid phosphatase It is generally conceded that the least bony response is noted in the pelvic bones Most of our cases, regardless of bony metastases, have been followed with x-ray examination of the pelvis at 6 to 12 month intervals Some who did not originally exhibit bony metastases did so after hormonal therapy, although they complained of no pain Following hormonal therapy there is usually a sclerosis of the bone characterized by increased density and a more sharply defined outline Temporarily the lesion in the bone ceased to spread in some of our patients, and in others it continued to increase in size, even though the patient continued clinically free from symptoms, gained weight and felt well We do not have any cases in which the bony metastatic lesion has completely subsided With continuous administration of synthetic hormonal therapy bony lesions do not entirely disappear from the pelvis, and patients after a delayed period begin to show evidences of increase in size of the primary tumor followed by some loss of weight but never to the stage of extreme emaciation as is seen without the treatment

Kahle,<sup>10</sup> Kretschmer,<sup>24</sup> Herbst<sup>17</sup> and Huggins<sup>14</sup> report histological study of prostatic cancer before and after hormonal treatment Most writers agree that there is a shrinking of the cells, that the nuclei become small and dark-staining and that the cytoplasm becomes vacuolated and indistinct after 6 to 8 weeks of treatment Herbst, reporting an autopsy 8 months after castration and administration of diethylstilbestrol, states that the prostatic mass was so small that it could hardly be recognized, but malignant cells were present microscopically in the tissue removed from the prostatic site Kahle used massive doses of estrogen in 7 cases and found microscopically in the surgical specimen in one case after two years of treatment that the stroma consisted only of smooth muscle and fibrous tissue

The hormonal factor, whether it be administered surgically, by castration, synthetically, with estrogens, or roentgenologically, by irradiation of the testes, acts in the same way. Some urologists prefer castration, others, stilbestrol. Surgical castration produces a more rapid and pronounced effect in relief of pain and nausea. Stilbestrol given in massive doses will produce a similar reduction of the serum acid phosphatase in the blood, a similar clinical response and similar local tissue changes. Where castration fails, there is no local regression of the tissues and little, if any, drop in the serum acid phosphatase readings. In those cases in which there is a temporary improvement and then a reversion to a continued uninterrupted malignant picture, the additional hormonal therapy is of little value. Dean<sup>23</sup> has found that after castration 45 per cent of the cases show as much or more androgen content in the urine. These cases represent the unfavorable ones. This is explained on the basis that the adrenal gland compensates for the testes, as it is the only other source for androgenic production. Dean reported that 11 out of 16 patients had an increase of gonadotropic hormones after castration, indicating an increased activity of the anterior pituitary gland. Such is not the case after estrogen administration, thus giving evidence that estrogens do not stimulate the pituitary gland. Herbst<sup>17</sup> has suggested that the failures may be due to the fact that compensation by the adrenals for the testes occurs. The result is that the pituitary becomes hyperactive and causes the adrenal cortex to produce androgens which act as carcinogens upon the prostatic epithelium and cause the prostatic cancer to grow again. This possibility may explain "delayed failures," described by Nesbit. The adrenals in some of these cases have been described as being four to seven times normal size. We have not encountered such enlargement of the adrenals at autopsy two years after castration.

There are *objections* to both castration and estrogen administration. Castration produces a loss of sex function and inability to perform the sexual act. Many patients complain of shrinking of the penis. This applies mostly to the younger group, especially in the sixth decade. None after castration have developed gynecomastia or painful nipples. The administration of stilbestrol by mouth is well tolerated by most patients, but in some patients even in small doses it causes nausea and vomiting. After estrogen therapy alone patients complain of loss of sexual power, shrinking of the penis and testes. Others complain of

anorexia swelling of the breasts and painful nipples. Especially after the administration of both castration and synthetic estrogens do we encounter breast complaints. Some men seen in our clinic have developed very large pendulous breasts, which appear like breasts of the female. Moore, Wattenberg and Rose<sup>27</sup> have made microscopic study of such breasts after diethylstilbestrol therapy, and they report a proliferation of epithelium of the ducts, an increase in the length of the ducts and hyperplasia of the connective tissue stroma. While only four or five of our patients have developed large breasts, more complain of sore nipples. The nipples become red, sensitive and erect and the areolar tissue pigmented. Some patients complain of pedal edema, cutaneous rash, pigmentation of the scrotum, abdominal cramps, feminine type of body, and three cases in our clinic have developed acute diabetes mellitus. Whether they have developed diabetes due to the therapy or due to metastatic lesions in the pancreas one can not foretell.

It is difficult to ascertain the *survival period* after estrogenic therapy for prostatic cancer. Hypothetically, castration alone should not yield as long a survival period as continuous use of estrogen, unless castration is followed by sudden and complete control of the cancer cell growth. By continued administration of estrogen a constant attack is made upon the malignancy. Castration plus continuous estrogenic therapy offers a more effective attack upon the lesion. We have instituted a program of different hormonal treatment in different years, namely, castration for the cases for one year, castration plus hormonal administration for two years, and, finally hormonal therapy without castration. It is too soon to know that obstruction was treated surgically wherever too much of urinary retention was present. It is too soon to anticipate which regime of treatment will be the most effective. Whether the malignancy plays a part one can not now state. One must wait until a series of cases are dead before an accurate statement can be made. We have patients who died anywhere from 1 to 9 years and 9 months after treatment by all of the combinations of hormonal therapy. Others are living and are apparently showing complete regression of the primary lesion, while others show stages of re-activation of the cancer within the first few years. We have several patients who have lived 2 to 6 years with apparently normal health and urinations after perineal excision of enough cancerous tissue to allow

tion Reports of occasional patients living 3 to 5 years after estrogenic therapy becomes less significant when one compares the estrogenically treated group with those treated surgically before the institution of hormonal therapy Emmett and Greene<sup>24</sup> in comparing their two series, one prior to estrogenic therapy composed of 326 patients and another treated estrogenically, composed of 220 cases treated by castration, showed about the same percentage of deaths during the first two years It is quite possible that the three, four and five-year survivals will show a greater ratio of living patients, and that estrogenic administration may prolong some lives Randall<sup>7</sup> followed a small series of five cases for eight years after castration and reported four dead and the remaining one showing metastases It will require several more years of experience by several clinics before an answer can be given as to prognosis and expectancy after estrogenic therapy

*Choice of Hormonal Treatment*—At present there is a difference of opinion regarding the time of administration, the quantity and type of estrogen to be used and whether it should be used with or without castration Bumpus, Massey and Nation,<sup>28</sup> and Emmett and Greene<sup>26</sup> prefer castration Alyea<sup>29</sup> prefers castration followed by small doses of stilbestrol Those who use estrogens prefer different compounds Herger and Sauer<sup>15</sup> have used stilbestrol extensively, Moore, Wattenberg and Rose,<sup>30</sup> diethylstilbestrol, and Kahle and his co-workers,<sup>10</sup> diethylstilbestrol dipropionate Zondek, Sulman and Sklow<sup>31</sup> claim that stilbestrol is destroyed by the liver while diethylstilbestrol is very slowly inactivated by the liver The dosage of estrogens varies greatly in the various clinics A few urologists recommend 10 to 20 mgms, while Moore, Wattenberg and Rose<sup>25</sup> give as high as 60 to 80 mgms per day The tendency is to give as small a dose as will be compatible with maximum effects In our clinic we are now giving 10 mgm of stilbestrol per day for two weeks and then reducing it to 1 mgm per day for continuous use Three of our patients have been unable to tolerate even 1 mgm per day because of the nausea and general uncomfortable feeling We must admit that as yet we have not reached any definite conclusion as to which type of hormone to give or the amount best tolerated to obtain the maximum effect Theoretically, biologists believe that since castration removes the brakes upon the action of the pituitary and allows stimulation of the adrenals to produce an androgen with a carcinogenic agent we should be able to compute an estrogenic dose that would

produce an anti-carcinogenic action upon the prostatic cancer and still avoid castration and estrogenic injury to the testes

Why some patients respond more readily to castration than others we do not yet know. A part of the answer must lie in the secretions of the testis, but we have no method by chemical or microscopic means to evaluate this testicular hormone. Herbst<sup>17</sup> suggests adding a high vitamin factor in the treatment of prostatic cancer, thus hoping to modify the soil in such a way that the growth of malignant cells will be inhibited. Experimental evidence would indicate that most vitamins stimulate cancer growth, but folic acid is thought to be antagonistic in its action. Patients who gain weight after castration do so because of increased metabolism and increased ingestion of foods containing many vitamins, but regardless of the added vitamins patients continue to die from the disease.

There is no general agreement as to when is the most opportune time to apply hormonal therapy. Stirling<sup>32</sup> and Nesbit<sup>16</sup> prefer to wait until pain develops. Our clinic belongs to the school which prefers to give hormonal treatment as soon as possible after the histological diagnosis is made, regardless of pain or metastases. Castration or large doses of synthetic estrogen produce the same clinical and tumor response. Castration alone is not followed by gynecomastia while stilbestrol alone or as a subsequent agent after castration often is.

#### SUMMARY

As yet no case of carcinoma of the prostate has been cured by hormonal treatment. The only complete control of cancer of the prostate in our clinic has been obtained by radical surgical excision early in the development of the disease. The majority of the patients with extensive prostatic carcinoma suffering pain from metastatic lesions are made comfortable by hormonal therapy. Castration and stilbestrol treatment produce the same results. Pain is completely relieved temporarily in at least 50 per cent of the cases. The general condition of the patient is greatly improved, and 66 per cent gain weight. Fifty to 75 per cent have a temporary return to normal or comfortable micturition. Twenty to 25 per cent are not benefited. Neither castration nor estrogenic therapy prevents the development of metastatic lesions. Some metastatic lesions in the lungs and one in the femur have been reported to show complete regression while no case of metastatic lesion of the pelvis



has been known to have completely regressed. Locally, the prostatic gland becomes temporarily softer and reduced in size. After 3 to 22 months, the prostatic tissue increases in size until death. Most bony lesions show an ebonization which may remain until death or may change to a characteristic osteoplastic picture. Patients who have a recurrence after a year or more do not have pain of severe degree, nor does the serum acid phosphatase frequently become elevated. Such patients run a progressive downhill course with asthenia and die without extreme emaciation. The data are at present inadequate as to prognosis of life, and so far any great prolongation of life is not substantiated by reports. The fact that life is made tolerable for 50 per cent of patients by hormonal treatment justifies the therapy and opens the doors for extensive future investigations which may lead not only to a cure of cancer of the prostate but also to the prevention of its development.

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## NEW ABSORBABLE HEMOSTATIC AGENTS \*

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WITH the end of combat in World War II the new hemostatic agents developed in various research laboratories, developed under the pressure of the emergency, were almost ready for general surgical use. The preliminary experimental work had been done, clinical investigation had confirmed the laboratory reports and enough observers in general and special fields of surgery had tested the materials to appreciate the possibilities of a new technique for checking hemorrhage. The clinical investigation already done included trial by military surgeons, both British and American, in several theaters of operation. Fortunately, the carnage ceased earlier than some of us had dared hope, and before complete comparative studies of the different agents could be made in combat zones. In civilian surgery, critical evaluation of these new agents may take somewhat longer, as hemorrhage which makes packing mandatory is, happily, less commonly encountered in peace than in war.

The novelty of these agents, stressed in the title of this presentation, may be questioned. The need for staunching of blood goes back beyond history and many techniques have been tried, discarded, tried again and accepted. As an example of the aphorism that there is nothing new under the sun, it should be recalled that in 1911 Cushing, who, as a neurosurgeon needs must be, was pre-occupied with hemostasis, not only advocated the use of muscle to accelerate clotting, thus anticipating thrombin, but also predicted that "fibrin from whipped blood might be so prepared that it could be immediately plastered on bleeding surfaces"—which is just the application of fibrin foam. As to another "new" agent, oxidized cellulose, it may be that Halsted\* encountered its fore-

\* The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University. The gauze and cotton were supplied by Eastman Kodak Research Laboratories, Rochester, N. Y. (U. S. Pat. No. 2,232,990) through Parke, Davis and Company, Detroit, Michigan. Presented October 16, 1945 before the Eighteenth Graduate Fortnight of The New York Academy of Medicine.

\* This reference in *Surgical Papers* William Stewart Halsted, Baltimore. The Johns Hopkins Press, 1924, was brought to my attention by Dr. Jerome Webster.

runner in 1879 for he writes that he observed that penghawar djambi was used quite frequently in the clinic of Billroth, particularly for checking hemorrhage in papillary cysts of the thyroid. This material consisted of the root hairs of the East Indian bullock tree and was said to be styptic. Certainly it was cellulose. Thus in the field of "new" materials, of the three selected for this discussion, only gelatin sponge deserves this adjective, and it seems wholly probable that careful study of the literature would turn up some early trial of this homely substance.

The impetus for the development of an absorbable hemostatic packing for lacerated vessels in a cavity or for application to surface ooze—two forms of bleeding which present somewhat different technical problems—came partly because of the development of thrombin, particularly the highly potent, purified, water-soluble form obtained from beef plasma by Seegers and his associates.<sup>1</sup> Their reports of its experimental use as a hemostatic spray appeared in 1938 and a year later it was used clinically with promising results. Again neurosurgeons were those most eager to develop a suitable technique for use of this aid to clotting. Their cotton patties were more effective when soaked in thrombin, but difficulty still arose when the patties were removed. Needless to say, the clots which close torn or cut vessels, large or small, are those on which ultimate hemostasis and wound healing depend. If these clots, formed rapidly because of the additional enzyme activity of the thrombin, are stuck to the cotton patty, bleeding naturally begins again, however gently the patty is removed. There was need, therefore, for an absorbable patty which could be left in place.

The first answer to the absorbable carrier of thrombin was human fibrin foam. This was only one of many developments as a result of the large scale study of the fractionation of human blood plasma undertaken in the Department of Physical Chemistry of Harvard University. Plasma in amounts suitable for this project were, as is obvious, available because of the Red Cross blood donations. From this source, fibrin foam was separated and processed to form a dry, porous, brittle, cream-colored textile—if the term may be allowed. Another fraction was human thrombin, slightly less potent perhaps than the bovine form but free of any suggestion of possible antigenicity. Extensive experimental trials in animals, mostly monkeys, were carried out, which confirmed the expectation that immediate control of bleeding from oozing surfaces could be achieved, that the wounds could be closed with impunity and the

the foam would be absorbed with a minimum of inflammatory response and of residual scar

Following this experimental work these two products of human blood were used together for hemostasis in neurosurgical procedures with highly gratifying results<sup>2</sup> Slight ooze in the closed cranial cavity may be a serious complication where a similar amount might scarcely impede wound healing elsewhere The challenge of the absorbable carrier of thrombin had been met for this special field

Controversy at once arose, as was to be expected, as to the advantage of thrombin of human origin Theoretically it was to be expected that bovine thrombin might have antigenic properties for humans The experimental laboratory studies on this point need not be discussed here The very large series of clinical cases in which bovine thrombin has been used without untoward effect, used in many instances more than once in the same patient, have led competent critics to feel that as it is employed it is without significant hazard \*

It was an obvious sequence of thought, once the properties of fibrin foam had been demonstrated, that sources other than human blood might offer absorbable materials simpler in preparation, more readily available and equally effective There was no priority in this concept, and a great many different substances were proposed Some of these were irritating Some preparations were unsuitable in texture, too friable, hard to moisten and difficult to handle Many suggestions were made as to the possibility of combining not only antibacterial agents with the absorbable materials for an additional safeguard in the wound, but even growth promoting substances to speed wound healing Imaginations ran riot at the possibility of achieving in one simple application a triple miracle—the control of bleeding, the prevention of infection and the acceleration of repair

These proposals became at once the subject of intensive study at a pace somewhat more brisk than was always consistent with the highest scientific critique With the new term "beach-head," the desire for quick practical hemostasis was obvious to laymen as well as to physicians Much of the work was done in various institutions under OSRD contract This, because of the policy of the Committee on Medical

\* On July 6, 1945 it was recommended by the Committee on Surgery of the National Research Council, Division of Medical Sciences acting for the Committee on Medical Research of the Office of Scientific Research and Development that bovine thrombin be made available to the armed forces

Research to disseminate information in related fields of study and so speed investigation and prevent duplication of effort, made it possible for one laboratory to receive and use as control materials under study elsewhere. It was for this purpose that Lattes devised a simple and reliable technique for testing absorbability and the irritant qualities of various substances in a small and inexpensive laboratory animal, the rat. Unsuitable samples could be eliminated by this means and the more elaborate operative procedures in larger animals, monkeys and dogs, could be reserved for the promising materials.

The second absorbable substance to be considered in this presentation is one of those proposed somewhat later than others, much later than the absorbable cellulose which has been the subject of our own investigation at Columbia. At the suggestion of the Committee on Surgery we had the privilege of seeing this early in its development. It is the gelatin sponge, or as it is now named to indicate its similarity to the human fibrin sponge, "Gelfoam." It was developed by Correll and Wise<sup>3</sup> in the Upjohn Research Laboratories. Gelatin is denatured by a process not yet made public, so that it is rendered slowly absorbable. The process prevents its immediate digestion in tissue fluids, but must not be carried too far or absorption is too long delayed. The satisfactory product is determined by the speed with which a standardized pepsin solution will dissolve a cube of the material. The finished sponge is a glistening white porous mass which is elastic and can be sterilized by autoclave. Moistened, it becomes absorbent and pliable.

When preliminary tests in rats had convinced the originators that the gelatin sponge was non-irritant and absorbable, experimental studies were then undertaken by Light.<sup>4</sup> A series of craniotomies was performed in monkeys. Bleeding was initiated and then controlled. The animals were sacrificed at varying time intervals and the tissues were studied by Prentice. The gelatin sponge combined with bovine thrombin was found to be an effective hemostatic, easily handled and in general similar to fibrin foam in rate of absorbability and lack of significant tissue reaction. Our own experience with this material entirely confirmed these findings, as did Light's later clinical trial and the experimental and clinical investigations of Pilcher and Meacham,<sup>5</sup> working under OSRD contract at Vanderbilt University. They report clinical trial of gelatin sponge and human thrombin in neurosurgery by sixteen surgeons working in eleven different clinics here and in Canada. In a total of 291 cases

there were eight unsatisfactory results. In 134 of these cases a comparison was made with fibrin foam.

It has seemed to us that one factor will influence the neurosurgeon's preference for one of these two carriers of thrombin, provided each is equally available. That factor is the ease of handling. Sterile thrombin solution must be made up in each case, constituting a time factor which, however, is of no consequence in a neurosurgical procedure of choice. Some time is necessary to moisten the gelatin sponge and mold it to express air from its meshes. This, however, can also be done in advance of the moment when it is to be applied. Some of the fibrin foam preparations when wet have been more friable than others. The nature of the bleeding is a consideration which may influence the choice of material. The gelatin sponge has more body and in our hands packed somewhat more readily into freely bleeding deep lacerations. Both substances controlled surface ooze and became adherent with gratifying rapidity.

Our own investigation of oxidized cellulose—or, in more accurate chemical designation—cellulosic acid, began in 1941. For some years previous to this we had been searching for a non-irritating absorbable membrane to assist in the prevention of adhesions, particularly in the repair of a tendon in its sheath. A number of substances had been proposed by Dr. Hans Clarke, Professor of Biochemistry, College of Physicians and Surgeons, but had not been found suitable. He had been apprised, in advance of publication, of the work of Kenyon and his collaborators in the Research Laboratories of the Eastman Kodak Company where oxidized cotton had been produced. This had been prepared by oxidizing long-fibered cotton with nitrogen dioxide which resulted in the formation of carboxyl groups—COOH—in the long carbohydrate chain. The physical and chemical properties of the processed cotton depended on the length of time of oxidation. The texture was somewhat altered and the material was soluble in dilute alkali. In its present surgical form—and this is true of oxidized gauze also—it is soluble in dilute bicarbonate of soda, 0.15 Molar solution, approximately the pH of the blood.

In this early stage of investigation it was proposed for use as a blood substitute. Accordingly studies were undertaken by Kabat, but with disappointing results from the standpoint of the usefulness of this possible cheap substitute for plasma. The material, in solution, introduced

in large quantities directly into the blood stream of rabbits had no deleterious effects, but it was eliminated, unaltered, too rapidly through the kidneys to be useful. This constituted, however, a convincing proof of the harmlessness of the material to the organism as a whole. Whether or not it would prove irritating locally in the tissues remained to be investigated and it was this study which Dr. Clarke proposed to us.

In our preliminary observations, published in 1943, small amounts of cotton, and later gauze and paper—all oxidized cellulose—were introduced into almost every tissue of the body in experimental animals. Nowhere, except in bone, was any untoward effect observed. In repair of a clean experimental wound of bone, or simple fracture, there was some delay in the early callus, as might be expected from the acidity of the material.

This demonstration of the absorbable and non-irritating properties of oxidized cellulose came just at the time when the hunt was on for carriers of thrombin. It was tried at once as such by Putnam of the Neurological Institute and later by Uihlein at the Mayo Clinic. Both authors reported favorably on it as an absorbable patty with thrombin added.

There the matter might have rested, if everyone had not—as was to be expected—immediately envisaged larger fields of usefulness in hemorrhage even more torrential than that usually encountered in craniotomies of choice. Sterile gauze, in a package which could be quickly torn open, gauze which was absorbable, seemed the answer to those hemorrhages of liver, for instance, in which ordinary packing was mandatory, packing to be removed later with what difficulty and what secondary bleeding. Therefore, and this time under OSRD contract, we embarked on the somewhat more dramatic study of the control of freely bleeding lacerations of liver, kidney and spleen. It was then that we found that *large* quantities of oxidized gauze could be introduced, as the small trial pledgets and the cotton patties had been, with impunity. It was then that we observed a phenomenon to which we had been blind before—that the oxidized gauze had a specific hemostatic action greater than that in controls of ordinary gauze. We had thought it enough to have packing which could be left in a wound. We found that we had something more. Oxidized gauze and cotton when used dry, turned black in a few seconds in the blood welling up into the material. This observation was then confirmed by demonstrating the affinity of the material



for hemoglobin in dilute laked blood. An actual chemical combination occurred. In staunching hemorrhage it was observed that a sticky, gelatinous mass was formed, *not* a clot, which filled the wound space. By twenty-four hours this mass could be lifted away, because of the thin film of fluid present between the under surface and the raw tissue. The true clots which had closed the vessels were not disturbed. No bleeding followed the removal of the gauze. It was therefore a suitable material for packing in the clean closed wound, but could also be used in the open infected wound, for immediate control of hemorrhage, to be removed, if the quantity was large, without causing secondary hemorrhage. Large dead spaces could thus be allowed to collapse early, and drainage would not be blocked. In the presence of any quantity of exudate spontaneous separation of the material could be expected.

Thrombin was, therefore, unnecessary as an adjuvant to oxidized cellulose. Moreover, it probably rendered the material less effective. Comparison of the hemostatic action of the dry oxidized gauze or cotton with the thrombin soaked absorbable materials already described showed the cellulose at least equally effective. Incidentally the potency of the thrombin itself is probably somewhat inhibited by the acidity of the gauze or cotton, a fact which led some earlier observers to comment unfavorably on these materials as contrasted with fibrin foam.\*

Just as in April 1944 the laboratory work had almost convinced us that clinical trial of gauze in large amounts was justified, a mandatory hemorrhage forced our hands. A torn internal carotid artery, controlled by emergency packing with ordinary gauze presented the difficult problem of what to do next, after the patient had been saved from bleeding to death on the table. With some trepidation, on the third day after the original packing, the wound was reopened in the operating room, the packing removed, the hemorrhage dramatically renewed and staunched, this time with oxidized gauze. The wound was closed. It might have been wiser to drain for forty-eight hours, for there was thin discharge from the lower angle beginning the 6th day, containing small black particles of unabsorbed gauze. No infection occurred, however, and most of the wound healed per primam.

This encouraged clinical trial in other fields than neurosurgery. The

\* So much confusion has arisen from this original misconception that in their recent publication Bailey and his associates give us credit for having had two forms of the material, an earlier one suitable for use with thrombin and a new product, to be used without it. This of course is not the case. We are still working with the substance as originally processed.

## COLUMBIA-PRESBYTERIAN MEDICAL CENTER

## HEMOSTASIS WITH OXIDIZED GAUZE OR OXIDIZED COTTON

*Total of Clinical Cases to Date*

Partial Hepatectomy	4
Liver Biopsy or Gall Bladder Bed	29
Retroperitoneal or Retropleural Tissue	30
Infected and Contaminated Wounds	8
Bone	9
Biopsy or Excision (Lymph Nodes or Tumor)	11
Amputation Stump	2
Thyroid	3
Tooth Socket	2
Nasal Cavity	16
Tonsillectomy	1
Rectum	1
Prostate	34
Kidney or Kidney Bed	11
Circumcision or Orchidectomy	3
Vaginal Wounds	18
Urinary Bladder	1
Neurological	115

TOTAL

298

immediate effective control of bleeding, the black sticky character of the material when blood soaked, the absence of evident acute inflammatory or foreign body response, and the absence of any systemic changes were all borne out. Our clinical cases to date are shown in table form.

It is understandable that a well trained surgeon would hesitate before deliberately leaving what looks like ordinary gauze in a closed wound. Moreover, the rapid black discoloration is disturbing at first. The bright red clot in gelatin and fibrin sponges seems much more orthodox. Also the open wound from which the gauze may later be removed looks untidy with a few particles of black jelly scattered here and there. Furthermore, fibrin foam may be used in other fields than neurosurgery, and Bailey and his associates<sup>7</sup> have just published 240 such cases. Trial of gelatin sponge outside the field of neurosurgery is undoubtedly in progress and should be.

The suggestion that oxidized cellulose, demonstrated by Heidelberger to be specific immune polysaccharide, might have antigenic properties for humans initiated examination of patients' sera for possible circulating antibody. None has been found. This investigation was also

carried out by Dr. Heidelberger, who, taking these findings together with the lack of any clinical evidence of sensitization in a very large number of cases—some with repeated applications—states that there should be no hazard on this account in the free use of the material.\*

In conclusion, therefore, one may say that three absorbable materials, all recommended for use by the Armed Forces before the close of the war, have now been shown to be equally bland in the tissues and to be useful in bleeding not easily controlled by the usual accepted techniques.<sup>8</sup> Human fibrin foam and gelatin sponge, "Gelfoam" are recommended for use with thrombin. Human thrombin has been available and has been effective. Bovine thrombin has been even more widely used without untoward reaction. Bleeding in patients with disturbance of the clotting mechanism may well need thrombin for control.

The third absorbable material—oxidized cellulose in the form either of gauze or cotton—is of vegetable, not animal origin. It is not recommended for use with thrombin. It is an effective hemostatic when used dry. It is easier to handle in brisk bleeding than either of the foams, and in an emergency requires only the opening of the package in which it has been sterilized. There is no evidence to show that use of any of the materials has unfortunate late sequelae—general, such as anaphylactic manifestations, local, such as fibrosis or adhesions, even in the peritoneal cavity. They are all apparently safe and useful. The practitioners of the art of surgery and—now that the emergency is over and leisurely evaluation is possible—time will make the final recommendation for the appropriate use of these agents. Each one has been already, without question, more than once a life-saving measure.

\* Personal communication.

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## CORRECTION

The Editor desires to inform all Fellows of the Academy and other readers of the Bulletin that the report of the death of Dr Edward D Truesdell, published in the December, 1945 issue of the Bulletin, is incorrect. The actual decedent was Dr P Edwards Truesdale. The Editor deeply regrets any inconvenience occasioned by this error.

BULLETIN OF THE NEW YORK  
ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MALCOLM ASHFORD, Editor

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1946

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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



MARCH 1946

INAUGURAL ADDRESS\*

GEORGE BAEHR

President The New York Academy of Medicine

**D**URING the year which has just ended, the Academy has sustained an irreparable loss in the death of its late President, William Worthington Herrick. During his brief incumbency of office, the general fellowship, unfortunately, had too little opportunity to appreciate his significant services to our Academy. Those of us who were privileged to serve as Trustees and members of the Council under his wise leadership soon learned to rely upon his calm judgment and to look hopefully to the future of the Academy under his strong and able guidance. It is with a feeling of sadness and deep humility that I undertake the burdens which he has relinquished.

Because of the scientific program scheduled for this evening's meeting, time is not available in which to report to you on behalf of the Trustees and Council concerning the activities of the Standing and Special Committees and of the various Sections of the Academy during the past twelve months. Annual reports dealing with most of these activities will be published shortly. I urge you to read these reports if you are to appreciate the ever-broadening influence of the Academy.

\* Delivered January 3, 1946 at the Annual Meeting of The New York Academy of Medicine.



and of its fellowship in the fields of public health, medical education and of clinical and scientific research

I am pleased to be able to report to you that the Academy has weathered the financial and other difficulties of the war period without a break in any of its basic functions. Due to generous financial assistance from some of our fellows and, above all, from members of the Lay Advisory Council under the Chairmanship of Mr Walter Gifford, our financial position has actually been strengthened and, in spite of mounting costs, the year 1945 has ended without an operating deficit. A substantial share of the credit for the stability of the Academy during these difficult years of the war belongs to the Director, Dr Herbert B Wilcox who, I am sorry to inform you, has announced his retirement on October 1st. Another large share of the credit goes to our well named Steering Committee under the Chairmanship of Dr Harold Mixsell.

The financial picture for the current year however is somewhat different. In spite of painful economies, the annual outlay for salaries has of necessity increased 35 per cent since 1940, other operating costs more than 20 per cent. Repairs which could not be undertaken during the four years of war can no longer be postponed. Personnel shortages which were tolerated by the Fellows and visitors to the Academy and its Library because of the war, now require prompt adjustment. Our Finance Committee, therefore, estimates that income from annual dues and from endowments this year will fall short of meeting our minimum budget by \$38,500. However, I am sure that we can continue to depend on Dr Mixsell's Committee and upon other Fellows and lay friends of the Academy to help us bridge the gap that lies ahead.

Three non-recurring items must also be met before the immediate needs of the Academy can be fully realized.

1 A sum of \$35,000 is required for the purchase of foreign books and periodicals for the Library which could not be secured during the six-year period of hostilities but which our agents overseas have been assembling for us during the war years.

2 Dr Mixsell's Steering Committee has collected \$300,000 for an addition to the Library, which is most urgently needed in order to provide additional stack space for the books which now fill all available shelves and overflow on to the floors and the cellar of the building and of several adjacent tenement houses belonging to the Academy. Of this sum, about \$190,000 has come from the pharmaceutical industry,

as an expression of its appreciation of the importance of the Library for scientific and industrial research. I am privileged, tonight, to announce gifts totalling another \$110,000 for this purpose from the Commonwealth Fund, from Mrs. Henry L. Doherty, and from the late Dr. Sara Welt Kakels. For these generous gifts, the Academy is deeply grateful. The goal has almost been reached, leaving a balance of only \$50,000 which is still needed to complete the amount required for construction of the building and for equipment.

It is regrettable that time does not permit more than brief mention of the efforts of the Academy to meet the overwhelming demands of returning medical officers for retraining in medicine. Almost one-fifth of all the grade A internships and residencies of this country are to be found in the hospitals of New York City. It was, therefore, to be anticipated that thousands of young physicians who had been taken into the military services after an accelerated medical school curriculum and a most abbreviated and inadequate internship should, upon demobilization, look to this City and to The New York Academy of Medicine for placement in hospital residencies, rather than for so-called "refresher" courses. Through its Committee on Medical Education, the Academy has served as a clearing house for the hospitals of the City. Many discharged medical officers have been provided with opportunities for training in medicine, surgery and the various specialties. But the flood of applicants has been overwhelming and the total picture, it must be confessed, has not been satisfactory. Much more must be accomplished in persuading the hospitals of the City to increase the number of their internships and residencies, cost what it may, and to reorganize them in such a manner as to make them a real educational experience.

Most of the 60,000 medical officers in the Armed Forces are young men. While all over this Nation, people debate the merits of new methods for the distribution and payment for medical care, by far the most important problem in this field lies right before us. We are confronted with a "lost generation" of young physicians, who plead for some help before they are forced to return to the private practice of medicine. Their neglect at this time will profoundly affect the quality of medical care in this country for several decades. Above all other responsibilities during the next few years, the Academy will dedicate itself to a solution of its full share of this vital problem.

hospital and health centers must be adequately staffed with competent personnel. At the present time there is not available, and the immediate future does not promise to provide a large enough body of trained and experienced medical and other personnel to warrant a rapid expansion of hospital facilities. We are currently confronted with the distressing example of the grossly inferior hospitalization and medical care provided for our veterans. As in every other effort to extend and improve medical facilities, we are compelled to recognize the numerous inter-related factors—physical facilities, economic resources, medical education and training, and public education—each of which has a profound bearing upon the other, and all of which, collectively, are essential to the expansion and improvement of the medical services.

The President's second recommendation proposes an expansion of public health, maternal and child health services. This, too, the Committee endorses in principle, with the caution, however, that experimentation is needed to avoid the sacrifice of valuable facilities and procedures which are already functioning. We are not here venturing into virgin territory. Public health, as well as maternal and child health have been the concern of the American public and of American government for many decades, and particularly during the last forty years. We already have many excellent facilities, some run by state and local official organizations, others by voluntary and professional groups. Whatever expansions are undertaken should be developed in relation to these existing facilities.

The President's third proposal, to advance and support medical education and research, the Committee on Medicine and the Changing Order also endorses in principle. Here too, however, governmental aid to medical education and research should be of such character that it fosters and supports, but does not direct and dominate. The Academy, through its Committee on Public Health Relations, has already taken its stand on these matters in a resolution endorsing, with some slight modification, the Magnuson Bill now before the Congress.

The President's fifth recommendation, that means should be devised for protecting workers against loss of wages resulting from sickness and disability, the Committee endorses without reservation.

There remains to be considered the fourth of the President's recommendations, namely, national compulsory medical insurance. To this recommendation the Academy is definitely opposed. As a result of the

studies of its Committee on Medicine and the Changing Order, the Academy is convinced that any scheme of national compulsory medical insurance at this time would lead to most unfortunate results affecting the health of the public, and the science as well as the practice of medicine

It is not possible, under the circumstances, to discuss this fourth proposal in the President's Message in any detail. The proposed scheme of prepayment of medical costs based upon the enactment of compelling legislation and the collection of tax moneys is deceptive in its simplicity. Our studies have shown that the problem of providing for extensions of medical care is far from simple, indeed it is extremely complex, for it involves not only readjustments in the care of the sick but also among other factors, the structure and content of medical education and the broad fields of social, industrial and preventive medicine. Payment for medical care through insurance represents only a fragment of the problem. It should be obvious that insurance cannot do more than spread a portion of the risk of costs. It cannot solve our medical problems, because it cannot create the services essential for improving and extending medical care. It will not of itself teach the public to appreciate or to utilize effectively whatever medical resources are even now available to it. Insurance is most certainly incompetent to raise the quality of medical practice.

On the contrary, there is a wealth of experience which shows that under compulsory medical insurance on a nationwide scale, though a larger number of people receive medical care, the quality of medical services rendered by the individual physician tends to decline.

Under our present forms of rendering medical care which the President indicates would remain unchanged, the direct payment for medical services by a third party, the insurance fund, introduces a fundamental disturbance in the attitudes of both the subscribers and the doctors. The patient is tempted to demand more attention than he requires. Still more serious is the temptation of the practitioner to add to his income by rendering unnecessary service. Excessive demand on the one hand and unnecessary service on the other inevitably result in superficial performance. The financial rewards for volume of service and the pressure of patients constitute a combination of influences which to many is irresistible. This has been the recent experience in New Zealand and it has been our own experience in the operation of

## Workmen's Compensation Insurance

Unfortunately, the alternative method of payment under an insurance scheme, namely capitation, whereby an annual stipend is paid to the physician for each insured patient on his list, likewise produces objectionable results. When the financial reward is fixed, some physicians are tempted to render as little service as possible.

Experiences abroad and in the United States by no means preclude the success of carefully organized prepayment medical insurance plans in this country. At the present time, however, we in the United States do not know how best to develop such medical insurance. We need a good deal of carefully planned and regulated experimentation. We lack experience not only from the actuarial angle but, what is still more important, from the service angle. We must realize also that we have no basis in our own experience upon which to estimate what the contemplated extensions in medical service are likely to cost. We do know from European experiences that under national compulsory medical insurance, even as the general level of medical practice is lowered, its costs are raised. Furthermore, in the light of our own political history, we must recognize that wherever there are available for distribution large sums of "government money," there also thrive political influence and political patronage.

The Academy's Committee on Medicine and the Changing Order is not concerned with maintaining the "status quo" in medicine. It has devoted several years to exploring new methods for correcting the many deficiencies in medical service. As a result of its studies, it is convinced that the problems involved in the improvement and extension of medical service to all the people of the United States are numerous and diverse, hence, the ways to their possible solution are, and must be, of many kinds. In the opinion of the Committee the expansion of medical services indicated in President Truman's first, second and third recommendations, with the modifications noted, would serve immediately to extend and to improve the quality of medical care rendered to our people, and to lay the foundation upon which a better organization of the medical profession could be achieved.

In opposing the fourth recommendation, calling for immediate nationwide compulsory medical insurance, the Committee maintains that the problem of payment can be solved by methods less menacing to the high standards of medical service which have developed in this country.

over the years. To this end it offers a series of inter-related proposals, designed not only to make more medical service available to our people, but also to improve its quality. These proposals are not easily summarized out of their context in the Final Report, but it is possible at least to indicate the diverse paths upon which the Committee believes we must travel if we are to reach an orderly solution of the many problems which today confront us.

The Committee recommends, among other things, that voluntary, nonprofit insurance be given a thorough trial as a means of providing medical services for low-income families through prepayment. At the same time it recognizes that plans of this nature cannot be expected to solve the entire problem, and that in certain instances, for example, when private resources are inadequate, government support, preferably in the form of federal or state grants-in-aid, will be required. The Committee holds further, that it may be desirable to conduct careful experiments at state and local levels with compulsory government insurance, so that we may have in the near future comparative experience with the relative values of voluntary and compulsory procedure.

In order to raise the quality and to round out the scope of medical care extended under any system of payment, the Committee favors not only a number of revisions in medical education, but the gradual extension of group practice. Under this form of practice, which promises far-reaching improvements in the organization of practitioners and specialists, doctors conduct a joint enterprise in medical care in close cooperation with high-grade hospitals, sharing a common plan of remuneration and responsibility for the quality of service they render. The group system is especially attractive to young physicians entering the practice of medicine, who have been accustomed to work together while in training as hospital residents, and who desire to retain their relationship to the hospital, with all its educational and professional advantages. Even those physicians who settle in rural communities should eventually be able, under a well planned system of medical care, to retain or establish such a relationship to a medical center.

It is essential, moreover, that medical group practice units be organized also in relation to teaching hospitals, since an extension of prepaid medical care to all people of low income must inevitably have important repercussions upon medical education and research. The medical schools, for their part, must change their methods if they are to train

doctors for a new form of medical care, and no form of medical care can afford to neglect the advantages to the patient of teaching and research

Because it is much more economical—not alone in terms of money but in human values—to prevent the occurrence of illness than to cure it, the Committee places special emphasis upon preventive medicine in all forms of practice. To the same end, immediate efforts should be made to provide basic public health services for communities which are now lacking in those services. The Committee insists also that further education and enlightenment are sorely needed by all groups concerned—by government agencies, by the medical profession, by private welfare organizations, and most of all, by the public at large.

What is wanted at this time, therefore, is not an overall national compulsory scheme, but a variety of studies and experiments conducted by smaller units at State and at local levels. In this brief statement, it has not been possible to do more than indicate the nature and variety of State and local programs which, with the help of governmental grants-in-aid, may form the foundation for a Nation-wide extension of comprehensive medical care. Specific recommendations as to how such pilot studies and experiments may be carried out will be contained in the completed Final Report of the Committee on Medicine and the Changing Order.

It is the conviction of the Academy that an evolutionary transformation of medical practice is essential if the benefits of modern medicine, and especially of preventive medical services, are to be made more freely available to the people. It is far better to proceed in a somewhat slower but more orderly manner than to expose the nation to the risks, as yet unmeasurable, which immediate adoption of national compulsory medical insurance would entail.

INTRAVENOUS HISTAMINE IN THE  
TREATMENT OF MIGRAINE\*

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**S**IR THOMAS LEWIS, in 1926, showed that the reaction to local skin irritation was threefold (1) Local reaction at the site of the irritant, (2) local release of histamine from damaged cells causing the formation of a wheal in the immediate area—and (3) a further release of free histamine into the circulating blood

Advances in the study of histamine and its physiological actions indicate that such reactions to cell injury may take place in many organs or tissues with consequent release of histamine in quantities much larger than that derived from small areas of the skin. Furthermore, it is generally believed that certain tissue aggregates or organs, remote from the site of injury, are particularly sensitive to histamine, and respond to its presence, even in minute amounts, by vasodilatation. These have been designated shock organs, characterized by their great vascularity, notably of capillaries, and include skin, liver, spleen, mucous membranes, (respiratory and gastro-intestinal tracts), lungs, endothelium and brain, through the cranial arteries and capillaries, especially external carotid, superficial temporal and occipital as well as middle meningeal and internal maxillary.

The second of Lewis phenomena, local wheal formation following irritation or injury, is a local vasodilatation and can be produced at will by the intradermal injection of histamine, especially in susceptible individuals, while larger amounts injected subcutaneously, cause in remote organs, reactions typical of the response in allergy. Similarly, release into the circulation of histamine by any mechanism, traumatic, thermal

\* Presented November 20, 1945 before the Joint Meeting of Section of Medicine and the Section of Neurology and Psychiatry of The New York Academy of Medicine and the New York Neurological Society. From the Presbyterian Hospital of the City of Chicago.



(either heat or cold), chemical, circulatory, or allergic, may in individuals over-sensitive to this substance, result in an organ response characterized in the first phase at least by vasodilatation and typical sequelae—notably asthma, urticaria, etc

Histamine in the circulating blood, regardless of the method of its production, remains for an extremely brief time, being rapidly taken out of the blood stream by the cells of various tissues, especially endothelium, where it causes vasodilatation and the characteristic response of the organ involved. Hence, quantitative determination of this substance in the blood is extremely difficult and unreliable, and few data are at hand regarding the concentration necessary to produce such reaction in sensitive and non-sensitive individuals

It has been rather generally accepted that the phenomenon of migraine is precipitated by the release of histamine into the blood stream as the result of an allergic reaction and that the major attack of migraine develops only in those individuals whose tolerance to histamine is low and who would be hyperreactors at some one of the phases, as the result of intradermal, subcutaneous or intravenous injection of this substance—(skin test or systemic response)

It has been the contention of many, including the authors, that there are two types of migraine, the vasodilated and the vasoconstricted. This is borne out by well recognized features of both etiology, and treatment of individual attacks. In a relatively high percentage of cases parenteral ergotamine tartrate administered early in the cycle, will ameliorate or terminate the attack, whereas there remain a substantial number who either obtain no relief or experience aggravation of their symptoms from this medication, regardless of giving it early or even anticipating the attack. Obviously the former are in a state of vasodilatation and respond to a vasoconstrictor. Furthermore many of these patients, unresponsive to ergotamine, experience prompt and sometimes lasting relief from vasodilators, particularly nitroglycerine, nitrites and nicotinic acid. Experience with alcohol indicates that many persons are certain to precipitate an attack of migraine with as little as one cocktail (vasodilators) while others obtain definite relief from one or two drinks

Recently, Atkinson,<sup>1</sup> reporting on twenty-one cases of uncomplicated migraine, found that contrary to his experience in Ménière's disease, he could not divide his patients into two groups by means of the

standardized intradermal histamine response, since he found no hyper-reactors, or as they are generally interpreted, no case of vasodilator mechanism, and that every one exhibited a primary vasoconstrictor mechanism. He and Wolff<sup>2</sup> advance the attractive theory that there may be a dual mechanism in migraine with *primary* localized cerebral vasospasm accounting for localized prodromes or aura, of sensory, motor, ophthalmic, and cortical origin followed by a more generalized vasodilation causing headache, and Atkinson advocates attack on the initial phase with a vasodilator drug (nicotinic acid) with the object of preventing the onset of the headache, rather than waiting for the secondary dilatation to occur and then treating that phase with a potentially dangerous vasoconstrictor.

Atkinson further suggests in his article (Dec 1944) that such cases might be successfully treated with histamine, and it is on such an investigation, begun in early 1943 that we are reporting. Our preliminary observations on thirty-four cases were reported February, 1945, with two years study of some.

Unfortunately, we cannot accept this excellent hypothesis in its entirety, since many of our objective findings are at variance with such a mechanism. Primarily, many sufferers obtain relief or amelioration of attacks by use of vasoconstrictor drugs *very early* in the attack—with the very first intimation of aura—or even in *anticipation of attacks* which can be predicted because of regularity of cycle, impending menstrual period, dissipation or indulgence in foods known to be harmful. Furthermore the commonly reported experience is that delay in availing ones-self of ergotamine results in diminished or total loss of effect. Thus, in some cases at least, therapeutic effectiveness would indicate *primary vasodilatation* and subsequently either vasoconstriction or loss of response to constrictor therapy. Wolff demonstrated the dilatation of temporal arteries during headache—and experimentally showed that the intensity of the pain was directly related to the amplitude of the pulsation, of the external carotid. Wolff<sup>3</sup> believes and states that pain also derives from sustained contraction of the muscles of the scalp and neck, which contract reflexly from the pain of vascular origin—the muscular spasm per se being painful if continuous, and is of the opinion that failure to obtain relief after ergotamine has contracted the dilated vessels is due to persistence of the contractions of the muscles.

To further study this aspect of the mechanism, we have instituted

scrupulous study of the retinal vessels in order to ascertain if any *reflection* of the state of the cerebral vessels (carotid and branches) can be determined. With the cooperation of members of the department of Ophthalmology, we have studied eye grounds during intervals between the attacks, and when possible persuade patients to present themselves to us, in the hospital or offices, at the first premonition of an attack. Careful observations with accurate notes upon the state of retinal vessels, are carried out at frequent intervals, in some instances without therapy—in others with our various therapeutic agents. Frequently with administration of intravenous histamine, typical headache of great severity will result, necessitating decreasing the rate of flow or its discontinuance, during which times frequent examinations of eye grounds can be carried out, observing the state of the vessels during prodromal stages, at height of attack, and when relieved by nicotinic acid or ascorbic acid.

Results showed no single case in which there was vasodilatation of the retinal vessels even when there was flushing of the skin due to intravenous histamine injection. A large proportion of the cases showed no observable change in the diameter or state of the vessels. However, a few cases showed very definite, and in some instances marked vasoconstriction of the arteries and arterioles of the retina, intermittent in character, and involving all areas of the retina visible to us. These patients were not hypertensive and examinations between attacks of migraine without therapy showed normal eye-grounds with no such contractions.

It would appear that the contention that histamine vasodilatation involves chiefly the branches of the external carotid artery, is correct. However, vasoconstriction observed in these few cases did indicate that at times the widespread vasoconstriction postulated in migraine may involve the ophthalmic branch of the internal carotid.

Our interest in the problem of treatment of migraine with histamine dates from the work of Shelden and Horton<sup>4</sup> on the successful treatment of Ménière's disease with, first subcutaneous, and later intravenous histamine injections, Horton's recognition and successful treatment of histamine cephalgia,<sup>5</sup> and during the early stages of our work we were greatly stimulated by two articles which appeared at approximately the same time. Miles Atkinson,<sup>6</sup> in May, 1943, discussed the similarity of migraine and Ménière's syndrome, and their relation to

allergy and histamine production, while in July, Rainey<sup>7</sup> described a number of cases of Ménière's which were unsuccessfully treated with subcutaneous injections of histamine, but were greatly benefited by its prolonged intravenous administration

Rainey's conclusions verified our reasoning. As previously stated histamine remains in the circulatory blood only momentarily, being taken up rapidly by the cells, in which it is normally found

Much confusion of thought exists regarding the mechanism of histamine therapy, especially with reference to the term "desensitization" which in this context is ambiguous and leads to erroneous concepts. Consequently we believe the term "desensitization" should be restricted to conditions of true allergy, or the anaphylactic status, in which antibodies exist as the result of previous exposure or reaction to an antigen, by whatever route, with the response to subsequent exposures characteristic to the shock organ or organs involved—(asthma, hay fever, urticaria, etc.)

While not allergists, we believe, as do immunologists, that an antigen must first, be protein in character, and secondly, consist of an aggregate above a somewhat loosely demarcated zone in the scale of protein degradation. Thus, albumin, globulin, and albumoses with relatively enormous molecules, are antigenic, with great immunological specificity, while ascending from the low end of the scale, amino acids, and peptone are non-specific and non-antigenic. They may be injected or absorbed through various channels without production of antibodies and without resulting anaphylactic reactions. Somewhere in the polypeptid range, this specific antigenic property makes its debut, and becomes increasingly potent and specific as each protein molecule assumes its characteristic configuration.

With these facts in mind, we can neither assume that histamine which is decarboxylated histidine (an amino acid) could produce a state of sensitization or allergy, nor that its parenteral administration can desensitize in the accepted meaning of the word.

Therefore, we must conclude that these individuals are not sensitized, but exhibit degrees of lowered tolerance to histamine, and that successful therapy results from the production of an increased tolerance, either physiological as in the case of alcohol, tobacco, caffeine and numerous drugs, or quite probably from the increased production of histaminase, which does not prevent the formation and release of hista-

mine, but is mobilized and available to neutralize or destroy that substance. Keeping further in mind the rapidity with which histamine disappears from the blood, it becomes clear why its long-continued administration intravenously, to the limit of the patient's capacity, often for a period of six to ten hours, will be more effective in creating an increased tolerance than repeated injections which result only in a very brief exposure to its action.

*Selection of Cases* We have used no patients in this series who could conceivably have headaches from any other cause, such as sinusitis, neuralgia of the face or scalp, hypertension, infection, skull injury, eye disease, or brain tumor. To date we have accepted patients only with headaches of great severity or those of moderate to great severity. Private cases have constituted the great majority, but a liberal grant of funds for hospitalization and all costs, has allowed us to draw from a large out-patient department those patients whom we considered as pure migraine.

The criteria for selection of migraine are definite but vary in intensity and actual occurrence. All doubtful cases have been rejected in this series. Migraine headaches are paroxysmal, usually unilateral, temporal and post-orbital, and characteristic of the condition is freedom from any symptoms between attacks. Headaches are usually, but not invariably, preceded by aura or prodromes, appearing from six hours or more to within a few minutes of the onset, involving particularly sensory cranial nerves, predominantly vision, hearing or equilibrium, taste and smell, with various cutaneous sensations, and at times objective changes, such as dryness of the skin or a distinctive body odor perceptible to others. Familial history is frequent, and numerous observers report that inheritance of migraine from the paternal side is usually more severe than from the distaff line. Evidence of allergy and of other allergic states such as hay fever, and urticaria is common, and to specific foods, notably chocolate. Freedom from attacks in pregnancy after the first trimester is almost universal. Attacks usually involve nausea and vomiting, or nausea alone.

Migraine equivalents are frequently encountered either as a complete change in pattern of the attack, or as totally unrelated to sick headaches. Post, and one of the authors (W. A. T.) in 1924 recognized that paroxysmal tachycardia was in practically all cases a migraine equivalent, or cardiac migraine, and collected nearly fifty cases in which

the tachycardia entirely replaced the typical headache, alternated, or for longer or shorter periods replaced one another Vaso-vagal attacks (Gowers' Borderland of Epilepsy) are largely constituted of prodromes or aura which fail to materialize as a full blown attack

Determination of specific food allergies by elimination diets is made difficult by a refractory period, such that, after partaking of food known definitely to produce an attack, the patient may thereafter for a period of from two to eight or ten days, further indulge without ill effect In our experience, skin tests for foods have been largely unsatisfactory, either as positive or negative criteria The remarkable variation in the results of skin tests for food parallels the unreliability of interpreting the results of *histamine skin tests* and in our experience both of these methods of investigation may be largely discarded

#### TREATMENT

All patients have been treated by the intravenous injection of 1 mg of histamine base as histamine acid phosphate diluted in 500 cc of isotonic sodium chloride solution Initially, three injections were given on alternate days Later four injections, and at present, five or more such treatments usually on successive days are given Injections are given very slowly, about five drops per minute, at the beginning, and the rate increased or modified according to the individual response, the entire procedure taking from three to eight or more hours When possible the rate is increased to thirty or even forty drops per minute, in which case three to four hours will suffice Blood pressure is taken every half hour, and any decided drop is considered an indication for reduction of the rate or termination of that treatment, usually temporarily Too rapid an injection will result first in flushing of the face, later the chest and shoulders, often tachycardia, and finally a typical headache, mild to severe, which may be relieved by slowing the rate, or by injection, directly into the tubing, or otherwise, of epinephrine or ascorbic acid (1,000 mg) The onset of urticaria or asthma is an indication for similar procedures

Gastric analysis, done in most of the recent cases, shows a very high acidity with a high amount of secretion, as compared with fasting or control aspirations With half hour aspirations or continuous aspirations the patients experience no distress, otherwise many complain of heart-burn which is relieved by alkaline powder or prevented by routine

TABLE I—CRITERIA FOR SELECTION OF CASES OF MIGRAINE

## I. HISTORY

## Paroxysms

Usually unilateral—post orbital, supraorbital or occasionally occipital

## II. PATIENT IS

Free of symptoms between attacks

Free of symptoms during second and third trimesters of pregnancy

Frequently allergic

## III. AURA

May involve all sensory cranial nerves, especially

II Scotomata, blindness, diplopia, hemianopsia

VIII Deafness, tinnitus, vertigo, equilibrium

I Smell

Cutaneous sensory, pruritus, subjective changes in temperatures

## EQUIVALENTS

Paroxysmal tachycardia

Viso-visual attacks (✓)

TABLE II

NUMBER OF PATIENTS	75
SEX—MALE	11
FEMALE	64
AVERAGE AGE	38 years
AVERAGE AGE AT ONSET	18 years
AVERAGE DURATION OF MIGRAINE	20 years
AVERAGE LENGTH OF ATTACKS	25 hours
(Excluding Cases of Migraine State)	

TABLE III—RELIEF OBTAINED

Relief	Mod	Severe	Very Severe	Total
COMPLETE, PERMANENT	12		18	30
COMPLETE, TEMPORARY	4		7	11
PARTIAL	13		12	25
NONE	5		4	9
TOTAL	34		41	75

(66 out of 75 experienced relief)

TABLE IV—TYPE OF INJECTION PRODUCING RELIEF

<i>Relief</i>	<i>Intravenous Most</i>	<i>Adjunct Histamine Most</i>	<i>Total</i>
COMPLETE, PERMANENT	27	3	30
COMPLETE, TEMPORARY	9	2	11
PARTIAL	22	3	25
TOTAL	58	8	66

58 patients received intravenous only

16 patients received intravenous plus adjunct histamine

frequent feedings and powder. Two hemorrhages from unsuspected ulcers have prompted us to careful histories and adequate acid control. Precautions must necessarily be taken in the long continued use of a substance having such marked effects on circulation and gastric acid secretion—particularly the danger of thrombosis in event of falling blood pressure and decreased velocity of blood flow. No cases were treated in which hypertension, or cardiac or renal impairment were found to exist, or in which there was evidence of mental or central nervous system disease. Evidence of increasing tolerance was almost universally present, in the rate of flow at which successive doses were tolerated. Many patients were unable to take more than 50-100 cc., usually because of severe headache, at the rate of five drops per minute, on the first treatment, and tolerated progressively larger amounts at a more rapid rate until the entire 500 cc. was taken. Only then was the course of treatment considered started, and four additional doses given.

Seventy-five patients with pure migraine have been treated, with an average age of 38 years (Table II). The average age of onset was 18, and attacks had lasted from 3 to 40 years—an average of 20 years. Not including three cases of status migrainicus, the headaches lasted 25 hours and occurred every 11 days. No patients were used whose attacks were so mild as not to interfere with their daily life or activities. The remaining ones were divided into moderately severe (34), and very severe, the latter group (41) including only those who were incapacitated for more than eighteen hours or whose headaches were so severe as to require opiates for relief.



## EVALUATION OF RESULTS

Evaluation of results has not been arrived at haphazardly, with each of us having possibly different standards or ideals, but from analysis of objective statements by the patients from a follow-up questionnaire sent every three months, with squares in which the current condition may be checked and returned in a stamped self-addressed envelope

This contains data as to dates of treatment, filled in by us with patient's name and hospital number They report *My headaches are Well—Better—Unchanged—Worse—* with other columns for *Frequency—Severity—Duration—Nausea and Vomiting—Prophylaxis* Data as to relation of relief to treatment *Hospital Treatment—Later Treatment* Space below for expression of own opinion regarding success or failure of treatment—of actual attacks, modifications of attacks, aura, etc

## RESULTS CLASSIFICATION

We have found 4 different types of response as far as relief is concerned

1 Those whose relief was immediate—complete and apparently permanent (up to 2 years 8 months)

2 Those whose relief was immediate and complete, but whose headaches recurred after weeks or months, and who were subsequently improved or relieved by subcutaneous injections of histamine or by repeating the intravenous program

3 Those who did not experience immediate relief, after the intravenous treatments, but who gradually obtained complete or satisfactory relief either spontaneously or by later subcutaneous injections of histamine

4 Those who obtained no relief

*Statistical Results* Seventy-five patients with very severe or severe headaches, indisputably migraine in character, were treated in this manner Immediate complete relief to this date, covering a period of more than 2½ years, has been obtained in twelve moderately severe and 18 very severe cases Complete temporary relief in 4 moderately severe and 7 severe cases, partial relief in 13 moderately severe and 12 severe cases, no relief in 5 moderately severe and 4 very severe cases That is, 66 out of 75 experienced a degree of relief, ranging from partial to total

*Other Results* It is interesting to note that migraine equivalents

respond as do the classical attacks. Two patients with frequent and verified attacks of paroxysmal tachycardia reported complete freedom from such seizures, one permanently to this date, one reporting freedom for two years, with gradual return of infrequent, mild and brief attacks synchronous with the reappearance of an occasional mild but typical migraine. She is anxious to return to the hospital for further treatment.

Unprompted reports of improvement during the two past hay fever seasons have been recorded, as well as some benefit in cases of urticaria and asthma, for which therapy was not instituted as such.

*Criteria for Prediction of Successful Therapy.* There is no royal road to the solution of this problem. Theoretically the vasodilator cases should respond to histamine therapy, but as Atkinson has shown, they may be few. Our results from histamine skin testing have been of little or no value, and we find ourselves totally unable to predict or promise satisfactory results from information obtained from any other sources such as character of attacks. The most satisfactory criterion is that of producing a typical attack by the subcutaneous injection of 0.1 mg. of histamine.

Our results have led to other speculation in interesting and distant fields. What is the role of ascorbic acid in ameliorating the attacks brought on by histamine? The introduction of 1000 mg. into the rubber tubing results in prompt and complete relief from the induced headache whereas similar therapy seems without value in an established spontaneous attack. Does the use of ascorbic acid either prior to or during histamine treatment nullify to any extent the desired result? The intriguing work of Simon L. Ruskin, demonstrating the enhanced effect of the ascorbic salts of calcium, ephedrine, epinephrine and benzedrine (drugs which constrict the nasal mucosa), over the effect of other commonly used salts of these drugs in overcoming histamine constriction of the bronchioles, may prove the key to the solution of some problems.

The logical conclusion following results obtained here, would indicate that long-continued intravenous histamine medication, presumably 24 hours at a time with controlled rate of injection up to the patient's point of tolerance, will be even superior to the present shorter method of injection.

This work does not in any manner explain the phenomenon of migraine, and is merely a manipulation for its relief, one step ahead of

TABLE I—DISCHARGE DIAGNOSES—1941-1944

PSYCHOSES	146
HYSIERIA	99
PSYCHOSOMATIC DISORDERS	86
MIXED PSYCHONEUROSES	77
PSYCHOPATHIC PERSONALITY	64
REACTIVE DEPRESSION	57
ANXIETY STATE	55
NEUROLOGICAL	33
OBSESSIVE-COMPULSIVE	17
EPILEPSY	16
HYPOCHONDRIASIS	10
PHOBIC STATE	3
MISCELLANEOUS	11
<i>Total</i>	674

time for out-patient work or visiting and carried on a practice outside. There were two psychologists and (last not least) three social workers who carried a heavy load in Out Patient and Ward. Much time is spent by the full-time staff in laboratory and clinical investigation. This will not be discussed here, suffice it to say that in the last ten years 75 papers have been published on various subjects. Teaching is also part of everybody's work, for we teach Harvard medical students, nurses, clinical psychologists, social workers and divinity students.

The plant was at first a ward shared with Neurology, where we had 12 beds and only one room for a disturbed patient. In 1941 the new ward was opened in the medical building where we have an 18-bed ward surrounded by medical wards and laboratories. This position in the midst of an active Medical Service is most important. There is no isolation, on the contrary, we meet medical men constantly and everywhere on purpose and by accident. Familiarity has bred mutual appreciation. There are a few exceptions but they are individual and incidental.

The ward is close to our research laboratories. It has 15 beds in an open ward for neurotic men and women and three beds in a small closed ward for disturbed patients. This small ward has a central station for a nurse who can observe all three beds at once. It is protected so that suicide is difficult and is isolated so that noise is not troublesome. There

TABLE II—PSYCHOSOMATIC DISORDERS

NEUROCIRCULATORY ASTHENIA	17
COLITIS	9
ANOREXIA NERVOSA	6
THYROID	5
ASTHMA	3
ARRHYTHMIS	3
DERMATITIS	3
ULCER OF DUODENUM	2
MISCELLANEOUS	8
<i>Total</i>	86

is a "continuous tub" for sedative hydrotherapy. The open ward for 15 patients has five single rooms and rooms for two or four. There is a large day room in the middle where meals are served at a long table, and where recreation is organized and occupational therapy taught. There is also a small occupational therapy room for noisy crafts. Four single rooms are used as offices for interviewing and there is a large class room for meetings of students, nurses and interns. The proximity of the ward to the research laboratories makes clinical investigation easy. The Out Patient is open five afternoons a week in the Out Patient building, where patients are seen by appointment.

The work accomplished in the last ten years has been in the Psychiatric Ward, in the Out Patient and in the laboratories. In the last four years we have had 674 patients on the Psychiatric Service (see Table I). These may be sharply divided into (a) the psychoses—146 in number, who were looked after on the small disturbed ward and usually made only a short stay, and (b) the psychoneuroses, who were on the large open ward and stayed from six weeks to three months. These two wards perform different services: the first takes the disturbed patients off the medical and surgical wards and cares for them in isolation with proper nursing; the second is for psychoneurotic and psychosomatic patients who come from the medical wards, from the medical and psychiatric Out-Patient departments, or from outside physicians and members of the staff. This latter group is our main study and it will be seen from the chart that we had more hysterics than any other type of neurosis. Psychosomatic disorders are a close second. The mixed psycho-

TABLE III—PATIENTS ON WARD B8

MEDICAL DISEASE WITH DELIRIUM	64
DRUG PSYCHOSES	52
DEPRESSED	34
SURGICAL DISEASE WITH DELIRIUM	31
SUICIDAL ATTEMPTS	25
EPILEPSY	14
MISCELLANEOUS	12
SCHIZOPHRENIA	11
HYSTERIA	10
NEUROSIS	10
MANIC	3
SYPHILIS	3
<i>Total</i>	269

neuroses also formed a large group and if combined with the anxiety states would make the largest group. They might well have been combined with the anxieties because a great many of the patients whom we label mixed psychoneurosis had presenting symptoms of anxiety attacks with hysterical and phobic symptoms as well. Our main therapeutic effort has been directed towards hysteria, anxiety states and psychosomatic disorders.

The psychosomatic disorders have been divided under various headings, as shown in Table II. First is neurocirculatory asthenia with forty-seven cases, because a special study was made of this disease with Drs Paul White and M. E. Cohen and patients were brought in from Army hospitals and from outside. This investigation is to be reported shortly in a series of papers. I will only mention here that from the psychiatric standpoint practically all of these patients could have been classified "anxiety state." We have had nine cases of ulcerative colitis on the ward and Dr. Lindemann has seen a great many more in the general hospital and handled them in collaboration with Dr. Chester M. Jones. The other categories are all in small numbers, but that does not mean that we have not seen a lot of each of them in consultation on the medical wards. It signifies that only a few of them have been sent up to the psychiatric ward for treatment. Usually it is a matter of bringing them out of their invalidism on a medical ward and bridging the gap to re-

turning to the outside world by means of the psychiatric ward where patients are up and about and there is active ward regime and much occupational therapy. The psychosomatic disorders are becoming a larger part of our work and this year we have admitted many cases of gastric ulcer and expect to take in more patients with gastrointestinal disease.

Table III gives a list of the patients brought to our small disturbed ward from the other wards of the hospital in the last 21 months. The larger number of these are patients from the medical wards who were suffering from delirium and therefore disturbing their ward. They have usually remained with us a week or ten days and then been returned. Many were not officially admitted to the Psychiatric Service and therefore do not appear on the list of discharged patients. The next largest number are the patients who have become psychotic from drugs. Some of these are acute alcoholics who have been brought into the Emergency Ward and sent up to our ward because of noisiness. There are not many of these because they are usually handled by other institutions. A larger number of drug psychoses are seen in patients who have taken barbiturates in excess or who have had sedatives or narcotics after operation and become delirious. Most of these remain on our ward only a few days and are returned to their own ward or discharged. There are a large number of patients both from the other wards of the hospital and from the Emergency Ward who have become depressed and who are brought over because there seems to be a suicidal risk. Patients from the surgical wards with delirium are usually postoperative and often are those patients in whom it was necessary to use large amounts of morphine to control pain. They make a short stay and recover rapidly if the morphine is stopped and paraldehyde used. The patients who had made suicidal attempts came from the Emergency Ward where they were given first aid and sent to us so that there would be no repetition of the suicidal attempt. These were soon transferred to mental hospitals. Some of our own patients with hysteria or other forms of psychoneurosis had to be transferred from the open ward to the small ward for short periods because of their behavior. It will be seen that this ward, although a small unit has a rapid turn-over and is a great service to the hospital in looking after the disturbed and noisy patients and by watching them effectively with the smallest possible number of nurses. Had these patients remained on their own wards, they would have each

needed three special nurses per day, whereas in a protected ward, three or four patients can be watched by one nurse and a great saving made for the hospital as well as an increase in safety for the patient

The Out-Patient department is a large, active concern under the immediate direction of Dr Erich Lindemann. In 1934 there were 475 new patients, the number rose steadily in the next five years to 880. Then with the decline of all departments of the Out Patient, shown in the years 1940-1944, there is a moderate dropping off in numbers, hitting a plateau of 720 new patients per year. The total number of visits makes a parallel curve, the plateau being about 3,200 visits per year. This is about  $4\frac{1}{2}$  visits per patient. Since about half of the patients are seen only once as a consultation problem, this means that the average out-patient is seen eight times. Even with this small number of visits we are able to do fairly satisfactory therapy and a large number of the patients report relief.

As to treatment I can make some brief statements. We do not use shock and we do not psychoanalyze patients. Many members of the staff have had psychoanalytical training, but the process of psychoanalysis is too long to use in the ward or out-patient department. Our therapy on the hospital patients can be roughly divided into (1) *living on the ward* with nursing, social service and occupational therapy regime, (2) all this plus *insight therapy*, which is given by use of interviews with the psychiatrist. In the last ten years we believe that we have learned something about what to do in this interviewing and what to avoid. We try to make the interviews specific and headed toward a definite *limited goal*. After the first two or three talks one is usually able to decide what these goals shall be. Unless such limitations are imposed, the interviews may degenerate into wandering conversations which scatter over the patient's whole life and which are not much use to the physician or the patient. To use Lindemann's word, we try to reach a solution of the *immediate predicament*. The patient is usually in some sort of a hard situation and this may be used as a starting point. In the light of this, we make up our minds what goal we want to achieve in therapy. We know that it is impossible to lift the whole psychogenic load from a patient's shoulders, but we also believe that it is "the last straw that breaks the camel's back" and that if we remove a few straws the patient may be able to carry the rest of the load. Therefore a limited objective is decided on and this is used as the central point in the inter-

view For example, with one woman, the objectives were to get her to have false teeth made and wear them and to get back to her job Having succeeded in these practical aims we had by the way touched on and helped some of her main psychological problems narcissism, inferiority and ideas of bodily pollution

If there is no immediate predicament that is easily worked on, one takes the presenting symptom and studies this from the standpoint of *stimulus and response* One studies what stimulus brings out the symptom and under what circumstances Bringing up example after example gives material that may bring insight to the patient We feel strongly that insight must come from the patient and not be supplied by the physician It is too often the case that telling the patient what is wrong with him psychologically (determined by the psychiatrist's insight) will upset him a great deal, either because the psychiatrist is wrong, or because the patient is not ready for that sort of information

A very important part of treatment is the *social follow-up* given by the physician and the social workers in the Out-Patient When the patient leaves the hospital he has made contact with a social worker who will see him in the Out-Patient This, if properly carried through, gives the patient a feeling of belonging to the group The hospital with its physicians and social service represent to some extent the family doctor upon whom he can depend and to whom he can return if he needs more help By this follow-up, especially through social workers, we have helped a great many hysterical patients who at first looked rather hopeless

In closing I would like to speak particularly about these hysterical patients, our largest single category of patients seen in follow-up We had thirty-two patients of whom thirty were improved This is a much higher percentage than is shown in other follow-up studies so I am skeptical as to its accuracy Probably the trouble is that in the patients who returned after receiving letters, there is an undue proportion of successes because they wish to return, whereas those who have received no help wish to avoid the doctors and the hospital Be this as it may, there are a lot of severe hysterics who have improved The other patients have not improved in as large a percentage

A large number of hysterical patients had very severe symptoms These are of the pseudoneurological sort, but there were many with sensory symptoms pain, headache and vomiting We believe in keep-



NAME \_\_\_\_\_

Hospital # \_\_\_\_\_

HEREDITY \_\_\_\_\_

Date \_\_\_\_\_

YEAR	MEDICAL DATA	SOCIAL DATA	AGE
1897			1
1900			4
1902			6
1904	FEARS	MOTHER DIED	8
1906	TANTRUMS "PLEURISY"	FATHER RE-MARRIES	10
1908	HEAD INJURY	" DRINKING	12
1910	APPENDIX OP	ASSAULT	14
1912	HEADACHE, PHOBIA AMNESIAS	M G H	16
1914	ADHESIONS OP		18
1916	FRIGID	MARRIED	20
1918		H ETAC PRECOX	22
1920	HEADACHE HYSTERIA	SON BORN	24
1922		DAUGHTER BORN	26
1924			28
1926			30
1927	NERVOUS CONVULSION	FATHER DIED	31
1928	PAIN, RUQ } D+C	STEPMOTHER IN HOME	32
1929	DYSMENORR } D+C		33
1930	HEADACHE } D+C		34
1931	CYSTOSCOPY D+C		35
1932	" D+C		36
1933	" D+C		37
1934	" D+C		38
1935	" D+C		39
1936	" D+C	SEX URGE +	40
1937	DEPRESSION OBSESSIONS	SON 2 ARTHRITIS ARIZONA	41
1938	ABD PAIN D+C		42
1939	DUOD ULCER DEPRESSED	M G H	43
1940	AGITATED	"	44
1941		STATE HOSPITAL	45
1942	PAIN, ETC	DAUGHTER'S MISCARRIAGE	46
1943	GALL STONES OP		47
1944		" PREGNANT	48
1945	DEPRESSED	" DIES	49

TABLE IV—LIFE CHART OF PATIENT

ing our diagnosis of hysteria in a narrow range, for those patients who are childish, self-absorbed and full of fantasies and who show amnesias and substitute symptoms for direct action in meeting situations, i e , make a primary gain by this conversion (Why it is always called "secondary" I don't know ) We avoid the loose term "anxiety hysteria," which to my mind includes many reactions of the conditioned reflex type and many which are merely exaggerations of normal, physiological responses to emotional stresses Severe hysterias are common and of those that we saw 90 per cent were in girls between thirteen and thirty Their paralyses, amnesic stupors, fainting fits, etc , were usually relieved during a stay on the ward, by maneuvering the situation so that they wanted to get well, or by suggestion We tried to keep them on the ward for only a short period and to return them home as soon as the main symptoms improved Then a long period of re-education began through the physicians and social workers in the Out-Patient It was this slow, laborious work of making a lasting friendship with the patient and using it for re-education that eventually brought them out of their hysterical mode of reaction A surprisingly large number of them returned after five or six years and told us that they were married, had children and were now happy and were having no symptoms They had grown up and were now acting like adults rather than naive children This is an important point in hysteria They must *grow up* so one does not know how much our therapy had to do with improving them and how much it was merely the lapse of years

On this point it has interested us to look up the past histories of some of the women who have come to us in their involutional period, with the symptoms of depression, obsessions and hypochondriasis Many of these showed hysterical reactions in their youth and one wonders if this sort of reaction at the age of 50 is not an ordinary fate for the hysterical patient, because we rarely see out-and-out hysterical symptoms after the age of forty and they are much more common under thirty The life chart of one of these patients (Table IV) shows that she was in the Massachusetts General Hospital in 1912 with hysterical symptoms and was diagnosed hysteria at the age of twenty-four The events that apparently precipitated her adolescent period of hysteria were the assault and the appendectomy at the age of 14. The operation gave her no relief from pain and led to another operation at the age

of eighteen for "adhesions." She then got along fairly well until her father died and then she had "nervous convulsions" and a syndrome consisting of pain in the right upper quadrant, dysmenorrhea and headache, which recurred once a year for the next nine years and was relieved each time by a dilatation and curettage. Added to this there were four cystoscopies. Nevertheless she went through these years and raised her two children fairly well. Then as her menopause approached she had an increased sex urge, which brought up a lot of anxieties about the sexual assault she had undergone at the age of thirteen, just before the appendectomy. From then on she went into a state of depression, obsession and agitation that at times led her to be hospitalized in a mental hospital. We are much interested in these patients and are collecting a series of them in the hope that we can throw light on the course of untreated hysteria.

The incidence of appendectomy in these hysterical girls is extraordinarily high. Of the 32 hysterical patients listed in this follow-up, twenty had had appendectomies, whereas among 100 student nurses there were only thirteen appendectomies. By keeping our eyes open for these young hysterics who complain of abdominal pain and are rushed into the Emergency Ward, we have been able to recognize a number of them before operation and in some we have relieved their symptoms by working out their troubles, which are usually adolescent fears related to menstruation and motherhood. Once recognized and with the diagnosis of hysteria in the record, they are much less likely to be operated on. Thus we hope to avoid starting hysterical patients on the operative habit which goes on so disastrously in many of them, as illustrated in the life chart.

I might have spoken about the cases of anxiety neurosis, about the neurocirculatory asthenia patients or about depressions, all are important and interesting but the hysterical patients are the most dramatic. They are difficult patients to work with and bring into play all our patience and skill, yet I am convinced that most of them are helped to an important degree. No follow-up system can prove this because one can always be skeptical and say that the patient would have become well if no therapy had been used. Nevertheless our experience leads me to believe that all the energy, hours and money spent on treating the psychoneurotic patients has been well spent, in terms of human happiness.

## BRUCELLOSIS\*

*Problems of Diagnosis and Treatment*

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THIS second invitation to address the Academy on the subject of brucellosis within 18 months signifies a growing recognition of the importance of this illness. In a lecture given on 19 March 1943 as one of the Friday Afternoon Lecture Series<sup>1</sup> the ground to be covered was essentially the same, i.e., diagnosis and treatment of this ill-understood infectious disease. Much material had to be omitted then because of limitation of time and the wealth of available material. The same handicap exists this evening. I will attempt to avoid extensive repetition but to fill in gaps and to add what seems most important of the new material that has become available.

## DIAGNOSIS

The diagnosis of brucellosis cannot be easily established or ruled out. It is one of the most difficult tasks in medicine. Unless one is very wary he may attribute to brucellosis all symptoms which the patient exhibits only to find later that, in addition to *Brucella* infection the patient also had a perhaps unrelated psychogenic or somatic illness. One must be constantly on guard against overenthusiasm in making the original diagnosis and against ascribing all symptoms which subsequently arise to the same infection. Conversely, before making a diagnosis of psychoneurosis, one should be sure that brucellosis has been ruled out as a major cause of symptoms. When the neurosis and brucellosis coexist the patient himself often adds to the difficulty of the diagnostic problem by unwillingness to accept the role played by the emotional state.

That brucellosis must be considered in the diagnosis of any obscure illness, including the neuroses, has been said times without number. It has been understatement. Since the disease is common, since it simulates

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a great variety of other illnesses, it seems more sensible to say that its possible existence always should be considered along with tuberculosis, syphilis, malaria, rheumatic fever and the like. Experience has taught me not to wait until all other possibilities are ruled out before thinking of brucellosis but to think of it early. Only in that way can active measures be undertaken to bring about early recovery or cure and to prevent perhaps a lifetime of relapsing acute illness or of continuous or intermittent chronic illness.

*Agglutination Test* Having allowed brucellosis the dignity of a place in our thought processes along with the more time-honored illnesses, it is then time to discard the long existent fallacy that all that is necessary is to perform the blood agglutination test—that a “positive” reaction proves brucellosis, that a “negative” one rules it out. Such oversimplification of diagnosis can rarely be successful in other illnesses. It is especially fallacious in brucellosis. The agglutination reaction is negative in the majority of chronic infections and very frequently in the acute illness. It should always be employed, obviously, along with the blood Wassermann, and other routine studies. Its value lies only in a positive finding. Rarely is one misled by a report of agglutination in a titer of 1:80 or higher, although cross agglutination may occur, usually in low titers only.

The report of a negative blood agglutination reaction means just that, i.e. nothing. If the illness is an acute febrile one the agglutination test should be repeated before the intradermal test is done. Agglutinins may appear as the illness progresses but they may be artificially induced by the antigenic reaction of the skin testing material. The report of agglutination in low dilutions of the blood serum only (1:10, 1:20, 1:40) should be viewed with interest and not discarded as unimportant. Another test within a few days to two weeks may show a diagnostically high titer. If not there is usually no reason to defer the intradermal test longer.

*Culture* Culture may be undertaken at any time—the earlier the better if one must depend upon it for ultimate proof. Properly done, cultural procedures may require as long as 18 weeks, including adequate study of inoculated guinea pigs. *Brucella* is among the most difficult of all bacteria to isolate. However, isolation of the organism is the one definitive diagnostic measure. It may be positive when all other tests are negative, as in the classical case of Alice Evans<sup>2</sup> which has been con-

firmed repeatedly Only the laboratory staffed by capable technicians, who are really interested in the isolation of this organism, should be used for the purpose Too often routine cultural methods which have virtually no chance of success are employed Like the agglutination test a negative cultural study is of no significance The percentage of positive cultures in the presence of active *Brucella* infection, especially with the abortus strain, is extremely small, even with the most meticulous technique such as outlined by Poston<sup>3</sup> Culture has the greatest chance of success at the height of the acute febrile illness with the melitensis strain, the least chance in the chronic abortus infection with low grade fever or no fever

The two other essential tests, the intradermal test and the opsonocytophagic test, should be considered together and done at about the same time for greatest accuracy If the intradermal test is done far in advance of the determination of the phagocytic power of the white cells, artificial opsonins, along with agglutinins, may be induced

*Intradermal Test* The skin test is best done with 0.1 of a cubic centimeter of undiluted suspension of heat-killed *Brucella abortus* organisms in a concentration of about 2,000 million organisms per cubic centimeter Use of a mixed vaccine is likely to result in an unnecessarily severe reaction because of the presence of *Brucella suis* or *Brucella melitensis* The technique and significance are entirely comparable to the intradermal tuberculin test A positive reaction indicates sensitivity to *Brucella* protein, acquired through infection It does not indicate whether or not that infection is still active The most important early error in interpretation of the cutaneous reaction lay in labelling as negative all those that did not react violently A skin reaction that becomes apparent by the fifth to seventh day and which persists for ten days or more is a positive reaction A negative reaction will show little more than a faint blush at this stage and will have faded completely within ten days Negative skin tests occur in a small percentage of *Brucella* infections, as proved by positive culture The significance of the positive cutaneous reaction is modified by the result of the opsonocytophagic test

*Phagocytic Index* The opsonocytophagic test must be performed promptly after the collection of 5.0 cubic centimeters of blood, accurately measured into a vial containing 0.2 of a cubic centimeter of 20 per cent sodium citrate in normal physiologic saline solution Every

hour that this specimen stands progressively reduces the phagocytic power of the white cells. Technique must be highly accurate. If a non-virulent culture of *Brucella* is used, phagocytic power of the white cells is relatively increased and the result proportionately inaccurate. The number of live bacteria ingested by each of 25 polymorphonuclear leukocytes gives the direct index of the patient's resistance to *Brucella* infection. In general, a low or moderate degree of resistance, coupled with a positive cutaneous reaction in a patient with symptoms suggesting brucellosis, points to an infection from which the patient has not recovered.

A high degree of resistance in the presence of a positive skin test is usually indicative of an old infection from which the patient has recovered. Of course, there are exceptions. A patient with a virulent infection may die of it even in the presence of 100 per cent of marked phagocytosis, as in the patient reported by Robinson. Presence of a focus of infection, such as salpingitis or cholecystitis, may prevent recovery regardless of the phagocytic power of the white cells. The test should never be construed as "positive" or "negative." Its only significance lies in the relative degree of resistance indicated.

#### SPECIAL PROBLEMS IN DIAGNOSIS

*Arthritis.* Arthritis is among the very special problems in any discussion of brucellosis, because it is a common manifestation of this illness and because it is rarely considered. Joint involvement in acute undulant fever was described by Hughes<sup>4</sup> in his monograph in 1897. In 1933 O'Donoghue<sup>5</sup> stated that Malta fever joint infections must be added to the legions calling for differential diagnosis of acute and sub-acute joint conditions. Simpson,<sup>6</sup> Hardy,<sup>7</sup> Goldfain<sup>8</sup> and others, have called attention to the occurrence of joint manifestations in chronic brucellosis. No one has sufficiently stressed the high incidence of arthritis of all types in brucellosis, nor the crying need for its recognition and treatment.

Two cases of arthritis will be described in some detail because they belong in the category of the supposedly incurable, progressive arthritides and because one has made a complete recovery and the other is in process of getting well. Both are progressive atrophic rheumatoid processes, one a classical Marie-Strumpel type. The degree of restoration of the hip joints in the first patient following treatment of the

Brucella infection, is clearly illustrated. The radiographs of the second patient shows similar joint pathology. Her clinical course to date suggests that an equally complete joint restoration can be hoped for.

*Case No. 1* The first patient is a young white male, aged 21 when he was first seen on 9 September 1941 in consultation with Dr. Edward Hartung at Post-Graduate Hospital. He had been bedridden for a year because of bilateral involvement of knees, hips, sacro-iliac joints and of the right shoulder, in an atrophic-arthritis process which had begun in 1935. It had been steadily progressive. Hip joints were approaching ankylosis. Fever had ranged from 99°F to 100°F daily, with a high point of 102°F. Tachycardia and lassitude had been present throughout. Sedimentation rate had been consistently elevated, ranging from 28 millimeters to 55 millimeters per hour. There had been a loss of 30 pounds in weight. He had had the advantage of the most expert diagnostic and therapeutic measures currently available: Vitamin D in massive doses, weekly blood transfusions, gold salts, irradiation of auto-transfused blood, streptococcus vaccine, salicylates, iodine and thiamine chloride parenterally, hydrotherapy, diathermy, and finally roentgen therapy had all been given adequate trial with little or only temporary improvement.

Brucellosis was considered as a possible etiologic factor because 1) Many cases of arthritis, of all types, apparently attributable to Brucella infection, had previously been seen, 2) A significant percentage of these patients had responded to specific Brucella vaccine, 3) The patient gave a history of consumption of raw milk from a herd of cattle subsequently shown to be infected, from 1926 to 1940, 4) All other possibilities of successful treatment apparently had been exhausted, 5) Experience over a period of nearly ten years had demonstrated that brucellosis must be considered in the diagnosis of any obscure illness. Blood agglutination test was negative, intradermal test was weakly positive on the fifth day, the visible palpable nodule persisted for more than twenty days, leaving little doubt of the significance of the reaction. The opsonocytophagic test indicated only slight resistance to Brucella infection with marked phagocytosis in 2 cells moderate in 3 slight in 9 and none in 11.

A therapeutic trial of Brucella abortus vaccine was begun on 29 September 1941. Physical therapy, consisting of massage manipulation and hydrotherapy, was continued. Within three weeks of the initiation





Fig. 1—Case 1 Marie-Strumpf type of rheumatoid arthritis, 20 March 1941, 3 years after onset

of vaccine treatment, improvement was noted, especially in the hip joints. On 20 October 1941 the patient was able to sit on the edge of the bed for an hour. Fever steadily lessened. Sedimentation rate did not consistently parallel improvement. By 15 November 1941, seven weeks following the inception of *Brucella* vaccine therapy, the patient was walking with the aid of crutches. The left hip was still fixed in exten-

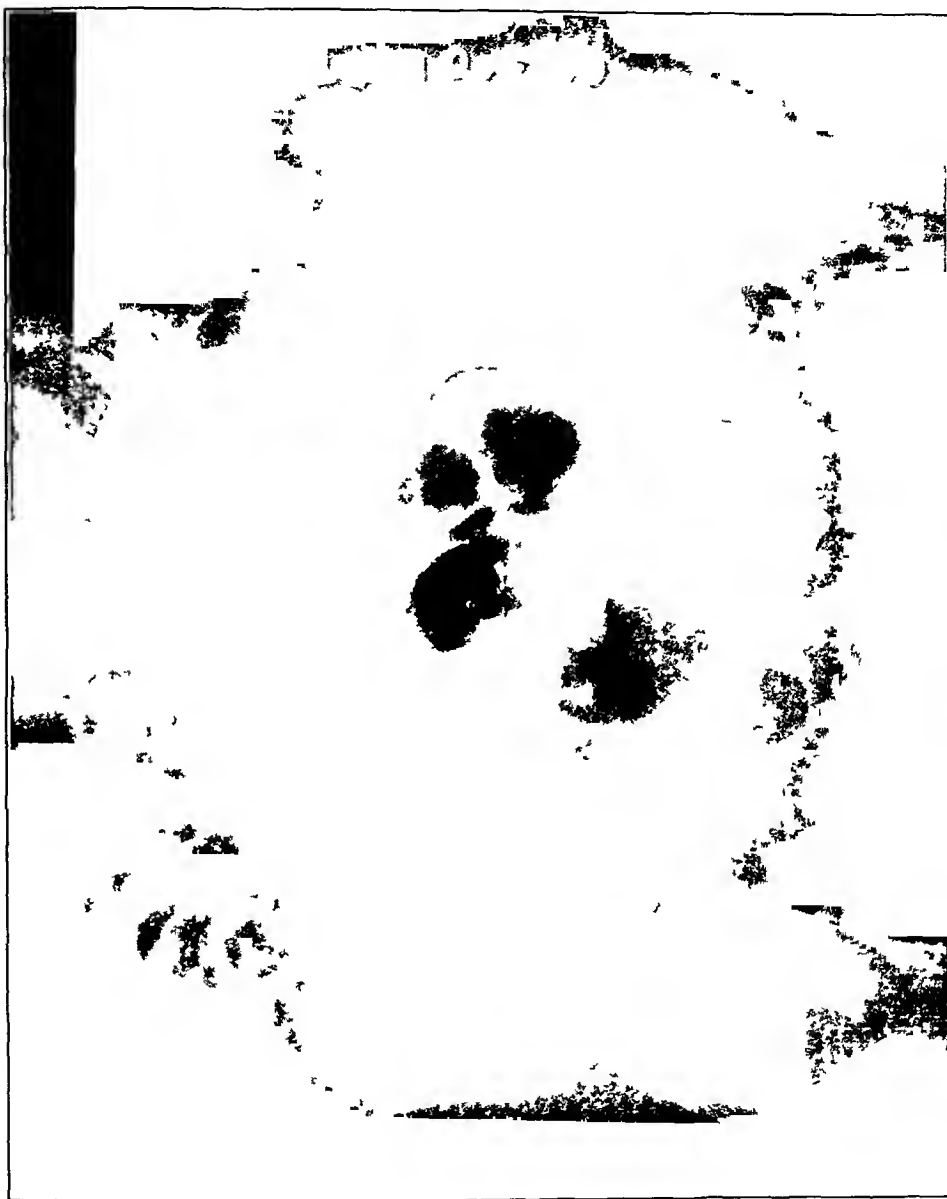


Fig 2—Case 1 Further progression 13 August 1941

sion The phagocytic index showed a steady increase (12-11-2-0 on 15 November 1941 and 16-9-0-0 on 6 December 1941) He left the hospital shortly thereafter The vaccine was continued, with no local or general reaction at any time By December 1942, 15 months later, he had sufficiently recovered to take a full-time job in a defense plant where he has been steadily employed since Vaccine treatment was dis-

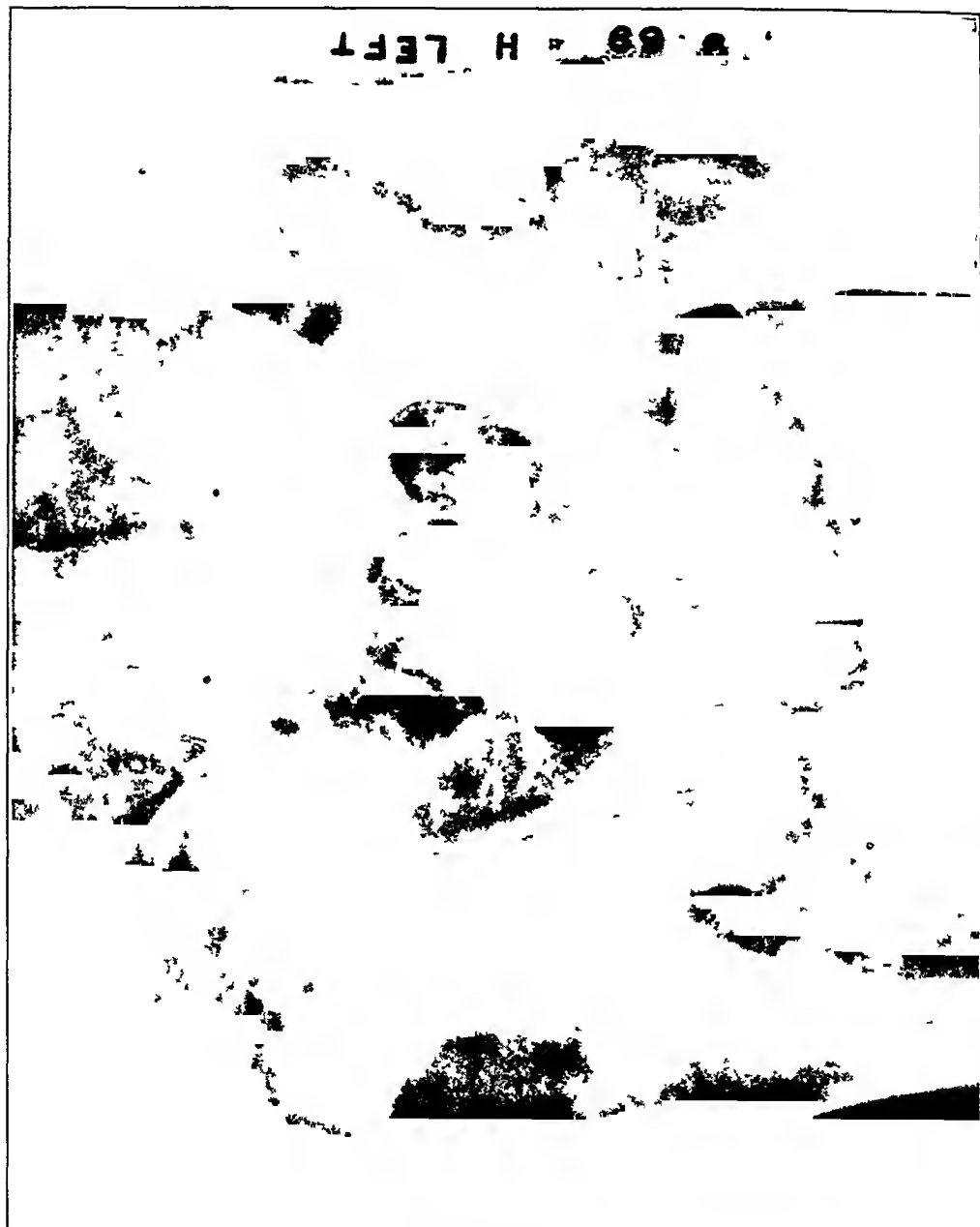


Fig 3—Case 1 Beginning reversal of process, 6 December 1944, 3 months following initiation of *Brucella abortus* vaccine therapy

continued in March 1944 and reinstituted in August 1944 following two attack of iritis, involving both eyes separately, attributed to brucellosis by his attending ophthalmologist

Review of x-ray findings revealed that definite x-ray changes had first been noted in March 1936, when the left sacro-iliac joint had showed chronic productive arthritis. In March 1938 both sacro-iliac

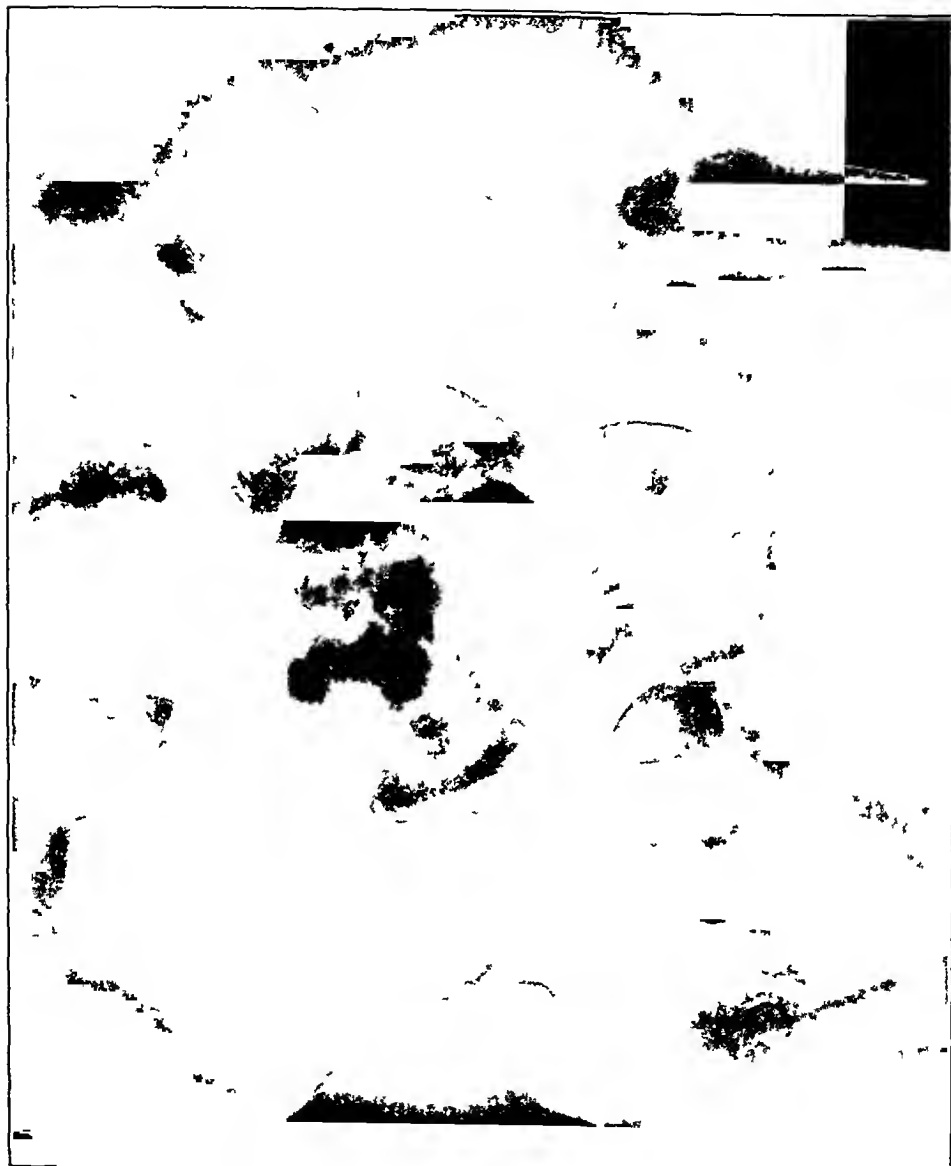


Fig 1—Case 1. Marked restoration of hip joints, 2 July 1942, 10 months following initiation of vaccine therapy

joints were about equally involved with no demonstrable involvement of hip joints. In November 1939 there was "considerable condensing osteitis about both sacro-iliac joints, with generalized decalcification of pelvis and spine, and little involvement of the posterior intervertebral joints, characteristic of Marie-Strumpel arthritis." From that time on serial radiographs had showed progressive involvement of the hip joints

and finally obliteration of the sacro-iliac synchondroses. The first visual evidence of reversal of this supposedly irreversible process was noted in films made in December 1941, three months after the inception of specific vaccine therapy. Films made in July 1942 showed almost complete restoration of hip joints.

*Case No. 2* This 19 year old girl was first examined by the writer in February 1944 in consultation with Dr. Andrew Campbell on the service of Dr. W. H. Irish at Post-Graduate Hospital. She had been well until ten years previously when there was a rather sudden onset of illness with chill and fever reaching  $104^{\circ}\text{F}$ , accompanied by a generalized rash, painful joints, headaches and prostration. The illness subsided after several weeks. She remained well for about a month after which all her symptoms returned for a period of six weeks. A diagnosis of rheumatic fever was made. Following recovery from this episode she began to have increasing difficulty in walking, with pain in both hips and stiffness of the knees. She had several recurrences of fever and rash and exacerbation of joint involvement and was twice hospitalized for several weeks prior to February 1936, first at Beekman Street Hospital and then at Presbyterian Hospital. During one attack the rash was thought to be scarlet fever. In October 1937 she was admitted to Welfare Island Hospital during another recurrence. Treatment had been continuous at out-patient clinics. She was admitted to Post-Graduate Hospital in April 1939 for treatment of her painful, stiff hips and knees, with a diagnosis of Still's disease, and was discharged to the outpatient department in May 1940, unimproved after physical therapy, Sutter fasciotomy, casts, manipulation and the like. She was repeatedly readmitted for manipulation to Post-Graduate Hospital between 1940 and 1943, with no clinical or radiographic evidence of improvement. Sedimentation rate was never over 36 millimeters per hour, blood counts were essentially normal except for relative lymphocytosis. Fever ranged from  $97.6$  to  $101^{\circ}\text{F}$  for periods of from four to six weeks, with intervals of from six to eight weeks, with a daily sharp rise and sharp drop.

Following readmission to Post-Graduate Hospital in March 1943 for physical therapy and manipulation under anesthesia, she developed severe headaches and recurrence of fever which persisted for six weeks. Dr. Campbell, the resident physician, then suspected the inadequacy of the diagnosis of Still's disease. He recalled that she had lived on a farm

and had drunk raw milk prior to the onset of her illness. Blood culture for *Brucella* was negative, as was the blood agglutination reaction. Intradermal test gave an atypical positive reading. Phagocytic index was reported as "negative" (meaning, no doubt, that there was little or no phagocytic activity of the white cells). A therapeutic trial of a commercial *Brucella* vaccine was begun on 16 December 1943. Improvement began within a few days following the skin-testing dose of vaccine, was clinically noticeable within two weeks and has continued. She was able to walk without assistance within three months. Hip joints regained about 60 per cent of normal motion as compared with 30 per cent of normal range previously. Knee joints improved to about 40 per cent of normal range, from 10 per cent. Phagocytic indices done serially indicated marked coincidental increase in specific resistance. Temperature steadily returned toward normal during vaccine therapy. In view of this splendid progress made under the mixed vaccine regime, I did not advise use of the usually preferable *Brucella abortus* vaccine. In July 1944 there was another febrile episode with temperature to 101°F and intense headache. During four days of sulfadiazine therapy toxic symptoms developed but temperature became normal, the fever recurring 24 hours after the drug was stopped. Penicillin was given to a total dosage of 500,000 units but with no effect on fever or headache. *Brucella* vaccine was then resumed, but with larger doses (2 cubic centimeters three times weekly). Within a week temperature subsided to normal and has remained so for the past 2½ months. Re-x-ray in June 1944 showed no change as compared with previous films.

The actual percentage of all arthritis caused by *Brucella* infection is not determinable. In rural regions, such as in the studies by Goldfain,<sup>8</sup> wherein arthritic patients have been life-long consumers of raw milk, it is to be expected that the percentage of *Brucella* arthritis will be higher than in a metropolitan region. Goldfain found that 51 per cent of 157 patients with arthritis also had chronic brucellosis, improvement "from moderate to marked degree and apparent cure occurred in a total of approximately 90 per cent of 23 cases adequately treated with *Brucella* bacterin." These patients all drank raw milk. I have repeatedly pointed out that the availability of pasteurized milk in large urban centers is not sufficient guarantee that their inhabitants may not be exposed to *Brucella* infection. The two obvious sources of infection of urban dwellers are raw milk consumed during vacations in the country,

or raw milk in childhood, or *certified* raw milk. Until recent months all certified milk in this region was raw. Finally, apparently as a result of various exposés of the presence of *Brucella* organisms in certified raw milk, one of the leading producers of certified milk has conducted an advertising campaign introducing *certified pasteurized* milk. On the basis of my own civilian practice among both rural and urban dwellers I would hazard the guess that perhaps 5 to 10 per cent of all arthritis is due to *Brucella* infection. Unfortunately, it has to remain a pure guess until some one, specializing in arthritis, will carefully study every patient encountered, for *Brucella* infection as well as for other etiologic factors. To determine the blood agglutination reaction only and to omit the most careful use of the multiple tests will give a false picture since the majority of patients with chronic brucellosis show no agglutinins in their blood, or in low titer only.

It will not be an accurate study unless patients representing a cross-section of the population of the United States are included—farmers, dairy workers, butchers, slaughterhouse employees, laboratory workers, rural and urban dwellers. It should be correlated with the history of ingestion of raw milk or its products, and of contact with cattle, at any time in these patients' lives. The infection may remain latent or sub-clinical for any number of years, apparently being lighted up in some patients by unusual fatigue, intercurrent illness or even by slight trauma.

Of my series of 427 patients with brucellosis, about equally divided between rural and urban dwellers, there were 74 (17.3 per cent) with atrophic or hypertrophic arthritis. Patients were not included whose arthritis may have been coincidental only. The evaluation was made on the basis of clinical study plus response to specific vaccine therapy. Cases seen in the naval service were not included. Cultural study of synovial fluid or blood was not usually undertaken because of the difficulty in persuading well-trained laboratory personnel of its importance and of the need to use the special cultural procedures for the isolation of *Brucella*.

*Salpingitis.* Of the vast number of other frequent or important localizations of *Brucella* infection time allows of discussion of but a few. Salpingitis is chosen for special mention because of its frequent occurrence in *Brucella* infection, its infrequent recognition, and its importance especially in the childbearing age. Cystitis and pyelitis along

with salpingitis, endocervicitis, endometritis, ovarian cysts and abscesses, will only be mentioned as sites of *Brucella* infection of the genito-urinary tract, frequently occurring but usually attributed to other organisms

Clinically, salpingitis due to *Brucella* infection differs from that of other origin in two important respects—its tendency to remain sub-clinical in many patients and its tendency to undergo spontaneous regression with frequent exacerbations. In the patient referred to elsewhere whose three abortions were followed by isolation of the organism, a most competent gynecologist reported negative pelvic findings within a week of the time that I had found the right tube markedly distended and tender. Ten days following this negative report there was recurrence of right lower quadrant pain and tenderness, low grade fever and malaise. Culture made diagnosis positive. In the absence of any attempt at or interest in cultural proof it is easy for the gynecologist to take refuge in such negative comments as, "I have never encountered a tubal infection caused by *Brucella*" or, "To the best of my knowledge most cases of salpingitis are still produced by a vicious little organism, first described by Neisser." Adequate cultural study in a large series of tubal infections still remains to be done.

Until such a study is undertaken the only data available must be furnished by isolated definitive cases of female genital infection, such as the one reported by me, and by various others, and by clinical evidence of its relative frequency. Among 192 female patients with brucellosis between the ages of 18 and 45, I found 24 cases of salpingitis (12.4 per cent) of apparently non-venereal origin. Only one yielded positive culture for *Brucella*. Few had the advantage of cultural study however. Gonococcal infection was excluded, as nearly as possible by blood complement fixation tests, cultures and smears. The clinical diagnosis of brucellosis was arrived at by use of the blood agglutination reaction, intradermal test and determination of the phagocytic index, plus characteristic response to therapeutic test doses of *Brucella abortus* vaccine. Five patients had exploratory laparotomies with no competent cultural examination of the operative specimens.

#### TREATMENT

*The Acute Illness* The acutely ill patient must have bed-rest because of the usual prostration, sweating, fever and various complications



such as joint involvement, respiratory tract infection, and the like. General supportive measures are, of course, indicated. Sulfathiazole, sulfadiazine, or sulfamerazine offer a way of bringing about remission but probably usually not of actual cure. Response to the sulfonamide compounds is usually noted within 48 hours or less. Two common errors are made in the use of sulfonamide compounds. The first is use of an insufficient daily dose and the second is its discontinuance after only two or three days of normal temperature range. Fairly full dosage (one gram six times daily for 2 or 3 days, then one gram four times daily) is indicated until temperature has remained normal for three or more days, following which dosage may be reduced to a half gram four or even three times daily, for two or three weeks longer.

It is wise to begin vaccine treatment about two weeks before discontinuance of the sulfonamide compound unless a very high degree of phagocytic activity already is present as the result of natural defense reactions. This is to guard against preventable relapse. If, during convalescence, a rising phagocytic index is found on frequent serial tests, and if it remains high for a period of months after apparent complete recovery, vaccine treatment is unnecessary at least at that time. A certain unknown percentage of acutely ill patients may have but one acute attack, with no subsequent acute exacerbations. Others develop chronic illness, too often confused with protracted convalescence. Unless their white cells possess adequate phagocytic activity, relapse must be considered likely and active measures taken for its prevention. It is my practice to repeat the determination of the phagocytic power of the white cells, at weekly intervals until the index has reached a satisfactory level and then biweekly or monthly, throughout active treatment. After discontinuance of vaccine therapy, the patient may be granted longer and longer respites from observation until a minimum of two years has elapsed in the absence of symptoms. Recrudescence of any symptoms possibly referable to brucellosis is an indication for repetition of the test, at any time. Relapse will rarely occur under this seemingly overly zealous regime. A significant fall in two successive tests must not be ignored since impending relapse is thereby almost invariably predictable, in the absence of actual cure.

In patients whose sensitivity to sulfonamide compounds cannot be overcome, or in those resistant to their effects, expectant treatment is justified only if the patient's general condition is excellent. The average

acute illness may terminate itself within three to five weeks or it may last eight to twelve weeks or longer. The mortality of about 2 per cent is not negligible, and it may be much higher in virulent outbreaks. In one such epidemic of *Brucella suis* origin a mortality of 25 per cent occurred. Development of irreversible processes such as *Brucella* endocarditis, not rarely reported, furnishes additional reasons for attempting to bring about remission as soon as possible. Use of Foshay's immune serum is usually effective in bringing about remissions in cases of less than four months duration, as may be transfusions of immune blood. Fever therapy may be successful in some. Huddleson<sup>9</sup> no longer advises the use of his filtrate of the mixed strains of *Brucella* in the presence of fever of 103°F or higher, nor is the use of any vaccine indicated at this stage, ordinarily. Foshay's detoxified (nitrous acid treated) *Brucella abortus* vaccine may be used in very dilute, reactionless doses when other measures fail and the febrile course is prolonged, however.

*The Chronic Illness* The first problem is to determine the degree of resistance already attained by the patient's white cells. If the opsonocytophagic test has recently been done in the course of the diagnostic study, that information is already available. Occasionally active infection persists even in the presence of a high phagocytic index. The organism may localize in any tissue in the body as shown by positive culture in living patients and post mortem. In general the patient with a low or moderate level of phagocytic activity, in the presence of clinical symptoms probably referable to brucellosis, should have the benefit of active specific therapy.

*Vaccine therapy* remains the method of choice for the initiation of treatment in the chronic infection. Recovery is brought about in approximately 75 per cent of cases, with marked improvement in an additional 15 to 20 per cent, under circumstances that leave no doubt as to its specificity. Recovery cannot be attributed to the non-specific effect of *Brucella* vaccine. If indeed one is so bold as to say it can be so attributed, then there must be in *Brucella* vaccine a most remarkable foreign protein of which the profession has remained ignorant. Phagocytic indices will almost invariably parallel the clinical course of the patient under treatment, rising as improvement occurs and falling in advance of or concurrent with relapse. A persistently high level of phagocytic activity is found in those who make uneventful recoveries and who remain well.

The type of vaccine is of importance. With Calder and others, I believe that the use of vaccine made from the abortus strain alone will result in less reaction, more prompt and lasting response, and a larger percentage of recoveries than from the use of vaccines of mixed strains of abortus and suis, or abortus and melitensis. There are, however, notable exceptions, as in Case 2 quoted above where a commercial mixed vaccine was used with such excellent early results. In this patient another exception was noted in that much larger and much more frequent dosage than average was necessary in re-establishing the course toward recovery.

The vaccine employed in nearly all of my 427 cases was prepared by the New York State Department of Health from a heat-killed strain of *Brucella abortus* isolated from the blood of a human patient. Reactions are kept to a minimum by use of whatever dilution is necessary, with the aim of desensitization by gradual increase in number of organisms. Phagocytic response seems best stimulated in this manner. There has been no similar vaccine commercially available except on special order. One of the leading makers of biologicals is in the process of marketing such a vaccine, however, and promises its availability by January 1945.

It is essential to vary the route, interval, dilution and dosage with the needs of the patient. In the vast majority the intramuscular route is preferable. In a small percentage intradermal administration, with or without concomitant intramuscular administration, produces more satisfactory increase in opsonic power of the white cells. In those who fail to achieve a high level of resistance, the intravenous use of the vaccine is indicated and usually is very effective. The optimum interval is that which produces the least reaction, the greatest sense of well-being, and the most marked phagocytic response. This varies from four to seven days but occasionally should be as short as two or three days. Dosage and dilution employed should be that which produces minimal reactions, with small increments. The dilutions usually needed are 1:10, 1:100 or 1:1000. The duration of treatment depends entirely on clinical and serologic response and tendency to relapse.

*Treatment of Localized Infections.* Discussion will be confined to arthritis and salpingitis, although infections of the gallbladder, prostate, urinary tract and other localizations are equally important when encountered.

Arthritis may not yield to *Brucella* vaccine therapy alone but recovery, especially in the presence of extensive damage, may be hastened or made more complete by judicious use of diathermy for the involved joint or joints, or, in some instances, by fever therapy. Spondylitis seems to yield better to fever therapy than do other complications of brucellosis, in the opinion of Phalen, Prickman and Krusen<sup>10</sup> of the Mayo Clinic. They quoted the earlier observation made by Thompson, Sheard and Larson who remarked that fever therapy is of value apparently through activating or heightening of the intrinsic mechanisms of the body rather than by bactericidal effect. They took cognizance of the fact that *Brucella abortus* organisms can survive 107°F for 24 hours *in vitro*. Their patients apparently had not had the benefit of adequate trial of *Brucella* vaccine however. I believe, with Simpson,<sup>6</sup> that fever therapy should be reserved for those patients who fail to respond to vaccine.

Salpingitis often will not yield to vaccine treatment alone. In fact the presence of this localized infection will frequently prevent recovery from the systemic infection, apparently serving as a persistent focus of infection until local treatment is added to the vaccine regime. In such instances ultrashort wave diathermy, using the Bierman or Gottesman vaginal electrode, in a majority of cases, will result in clinical cure of the tubal infection, which is usually then followed by complete recovery. High local temperatures and prolonged treatments are necessary. Surgical removal does not necessarily accomplish cure. Too many tubes and ovaries already have been sacrificed, as was formerly true in gonorrheal infections, not to re-emphasize this point vigorously. The infection itself produces so great a number of cases of sterility through tubal infections and abortions that every conservative means should be utilized to avoid the certainty of sterility through needless sacrifice of tubes and ovaries.

Vitamin B Complex probably plays a role in the recovery from the chronic infection through its recognized ability to increase the phagocytic power of the white cells. Its use should be routine. I believe not only during active treatment but for a long period thereafter. Other useful measures in the chronic illness include the sulfonamide compounds in a small proportion of patients, Foshay's detoxified vaccine and fever therapy in those cases refractory to vaccine therapy.

There still seems to be some reason to hope that penicillin or other

mold derivatives such as streptothrycin or streptomycin will prove to be bactericidal agents. The early work of Walter Kochalaty<sup>11</sup> at the University of Pennsylvania gave encouragement to the belief that penatin would be effective in human infections. However, he was unable to reproduce his earlier favorable findings. The early literature on penicillin has yielded only negative evidence of its value, with one noteworthy exception. Tsun Tung,<sup>12</sup> reporting his observations on the *in vitro* action of penicillin alone and in combination with sulfathiazole, stated that certain strains of *Brucella* had proved to be susceptible to penicillin, and that the effect was enhanced by sodium sulfathiazole. No clinical application of his idea has come to my attention. H. F. Flippen<sup>13</sup> of Philadelphia has used the material in several patients with arthritis whose agglutination tests were positive with no striking results, but in no case of brucellosis with a positive culture. Andrew Campbell<sup>14</sup> administered 500,000 units of penicillin to the patient described as Case 2 in the midst of a febrile relapse but with no improvement.

#### COMMENT

Many problems difficult of solution are encountered in the diagnosis and treatment of brucellosis. The major ones consist of the lack of a single uniformly definitive diagnostic measure, the failure to use and to correctly interpret the multiple tests, the tendency of brucellosis to simulate numerous other diseases, and the present lack of any truly bactericidal chemotherapeutic agent. However, not the least of the problems are caused by the emotional states precipitated by (and in turn aggravating and perhaps preventing recovery from) this debilitating and often frustrating disease. The patient's unwillingness to abandon the solid ground furnished by an earlier diagnosis of a somatic illness for what they consider to be the less tangible and more onerous diagnosis of neurosis, adds to an already complicated problem. As physicians, our own understanding of the mechanism of psychosomatic conditions is too incomplete to expect patients to accept readily our concepts of the psychic and somatic components of disease and to cooperate in the psychotherapy of the psychogenic, along with specific therapy of the infectious process when indicated. Intelligent management of both components are vital to success in some of these patients, however

## SUMMARY

The role of *Brucella* infection in the etiology of various common infectious processes, along with diagnostic and treatment problems, is discussed \*

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\* Opinions expressed are those of the author and do not necessarily reflect those of the Medical Department of the Navy or of the naval service at large.

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BULLETIN OF  
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APRIL 1946

THROMBOSIS AND EMBOLISM

*A Preliminary Report on the Comparative Results of  
Femoral Vein Interruption and Dicumarol Therapy\**

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CONSIDERABLE progress has been made on the thrombo-embolic syndrome during the past decade. It has long been established that there is a direct association between thrombus formation in the deep veins of the legs and pulmonary embolism. Evidence points to the leg-veins as the source of these thrombi in approximately 95 per cent of the cases. Patients ill enough to remain in bed, following surgical procedures, medical disorders, parturition, or trauma, are, under certain conditions prone to develop thrombosis in the leg veins. Occasionally, thrombophlebitis occurs in ambulatory individuals without known infection or illness. Instances of sudden death in a patient apparently making a satisfactory convalescence are familiar to everyone. Prolonged invalidism following phlegmasia alba dolens has long been one of the serious sequelae of parturition and surgery.

Efforts have been made to reduce the incidence of complications

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from inflammatory reaction in and about the deep veins and lymphatics of the legs. Contributions on the subject have dealt with etiological factors such as trauma, infection, protein levels in the blood and stasis in the veins. Too much stress has been placed on the origin of these thrombi in the pelvic veins following parturition, gynecologic operations, and prostatectomy. This, I believe, has delayed progress on the more serious condition of thrombosis in the deep veins of the legs. Posture, exercises, better surgical principles, and other factors have reduced the incidence of thrombosis and embolism. In spite of these precautions, there still remain definite problems to be solved in this field.

Homans<sup>1</sup> has called attention to "bland thrombosis" of the leg veins and Ochsner and DeBakey<sup>2</sup> have emphasized and confirmed this phenomenon and suggested the term "phlebothrombosis" to distinguish this condition from the usually recognized inflammatory thrombophlebitis. The most important reason for distinction in these two types of thrombosis lies in the fact that the non-inflammatory thrombus is loosely attached to the vein and is the chief source of serious pulmonary infarction. Part or all of a complete cast of the long deep veins of the legs may be deposited in the pulmonary arteries in a sudden manner causing death within a few minutes. If the detached thrombus is less extensive, a typical infarct in the lung occurs. It is well known on the other hand that in the fulminating, acute, inflammatory thrombosis of the leg veins associated with pain, fever and swelling of the leg fatal embolus is less likely. This is probably due to the fact that, under these circumstances, the thrombus is firmly attached to the lumen of the veins by inflammatory reaction.

The mechanism of the embolic phenomenon has recently been discussed by Chapman and Linton.<sup>3</sup> They have demonstrated that straining, as in defecation, superimposed on inspiration, changes the venous pressure in a manner favorable to the emptying of the veins in the legs. It is well known that many fatal emboli occur during the use of the bed pan.

We have frequently observed that, seemingly unquestionable bland thrombosis has often gradually changed into thrombophlebitis. Whether this is a transitional type of the disease, it is difficult to determine. I am sure that we do have the two typical extremes of the non-inflammatory phlebothrombosis on the one hand and the acute inflammatory thrombophlebitis on the other. In the former or more dangerous type from the

standpoint of embolism, we have little general reaction, little if any swelling of the leg and a minimum of tenderness or pain. The diagnosis in this variety is most often made after infarct has taken place. In true phlegmasia alba dolens, we have an acute onset of pain and swelling in the leg associated with fever, leukocytosis and elevated sedimentation rate. In this type, the diagnosis is obvious and easy and emboli to the lungs rarely occur. Between these two extremes we have all gradations of the disease. Bland thrombosis will often produce dilation of the superficial veins of the leg and foot—a slight cyanosis and a mild discomfort in the calf muscles on dorsiflexion of the foot (Homans' sign) and perhaps a slight swelling above the ankles. If infarct occurs with or without chest pain, there will be a typical mild elevation of temperature, pulse, and respiration at the same recording on the clinical chart. One needs nothing more than these minor indications for the institution of proper therapy. Under these conditions, whether the femoral vein is interrupted or not, there may follow a gradual increase in swelling, pain and tenderness in the leg, with more or less general reaction as observed in the typical inflammatory form. It is my belief that this transition from a bland to an inflammatory process may be more common in colder, damper climates than in warmer, drier zones.

The fact that our peak incidence of thrombosis and embolism occurs in the winter months (33 per cent) and our lowest incidence during the summer (19 per cent) would seem to support this contention.<sup>4</sup> Also, it would appear that fewer of the cases of phlebothrombosis develop into thrombophlebitis in New Orleans than in Boston. Furthermore, it seems that thrombophlebitis may run a milder course and is more amenable to sympathetic bloc in Ochsner's hands than in ours. There seems to be little if any variation in the type of patients admitted to the white wards of the Charity Hospital in New Orleans and to the Massachusetts General Hospital.

One of the factors of great importance in the discussion of this subject is the age of the patient. In our clinic only 5.7 per cent of the patients with thrombosis and embolism were under 30 years of age—an additional 12 per cent were between 30 and 40, leaving a total of 82.3 per cent above the age of forty. The largest group of patients with thrombosis of the leg veins was in the fifth decade or 25.3 per cent and the next in the sixth decade 22.9 per cent. Actually these figures begin to be slightly misleading at this point since the peak of admissions to the

hospital is during the fifth decade. The ratio of patients treated to the number with complications of thrombosis and embolism rises with the age of the patient. In an effort to determine why we were recognizing a greater percentage of this phenomenon in our clinic, a comparative analysis revealed that the patients admitted in 1943 averaged eight years older than those treated in 1930. The relative frequency of thrombosis and embolism in the older age group became so apparent that a number of the aged were protected from embolism by prophylactic femoral vein interruption.

There are two definite methods of preventing fatal embolus available at this time. The use of anti-coagulant drugs such as heparin and dicumarol are effective if properly used and there are strong advocates of this method<sup>5, 6, 7, 8</sup>. There are definite contraindications to the use of these drugs and the greatest care must be exercised in this regard. Heparin is expensive but has the advantages of rapid effect and of being inactivated quickly by protamine. It is of tremendous value as an adjunct to dicumarol during the lag period of the first 48 hours of treatment. Also, it is important after femoral vein interruption if minor infarcts occur from uninterrupted veins. Dicumarol has been used to some extent by Butsch and Stewart<sup>6</sup> preoperatively but the majority of pioneers in this field have felt it safer to use it after operation. Interruption of the long veins of the leg is the other chief method at our disposal at this time.

Up to October 1, 1945, we have interrupted the femoral veins on 816 patients at the Massachusetts General Hospital. These have been done for the following reasons:

- (a) Definite signs and symptoms indicating thrombosis in the leg veins, 47.3 per cent
- (b) Signs of infarct in the lungs, 34.4 per cent
- (c) Prophylactic interruptions in patients whose age and acute disorder would indicate a high probability of thrombosis during their treatment, 18.3 per cent

There has been an increasing tendency to interrupt the veins in both legs if any is done. This is due to the fact that we have frequently found thrombi on the supposedly normal side. We are further reassured of the safety of this procedure since interruption of the normal or uninvolved vein produces no appreciable disturbance to the patient. Swelling of the extremity after interruption of a thrombosed vein will vary some-

Table I—INDICATIONS FOR FEMORAL VEIN INTERRUPTION

	1937-1942	1943	1944	1945 (3/4)
Leg signs as first symptom	120 59.0%	93 56.3%	117 41.8%	57 33.7%
Chest pain as first symptom	82 41.0%	57 34.5%	91 32.5%	50 29.6%
Prophylactic interruption	0 0	15 9.2%	72 25.7%	62 36.7%
	202	165	280	169

Table II—FEMORAL VEIN INTERRUPTION  
 Massachusetts General Hospital—1937 to October 1, 1945

	Patients	Veins	Unilateral Interruption		Bilateral Interruption	
1937-1942	202	280	124	61.0%	78	39.0%
1943	165	299	31	19.0%	134	81.0%
1944	280	554	6	2.1%	274	97.9%
1945	169	335	3	1.8%	166	98.2%
Total	816	1468				

what depending on the duration, the extent, and the inflammatory element in the thrombosis. If the vein is interrupted prophylactically, there is so little post-ambulatory swelling that it is hardly noticeable. In the past two years less than 2 per cent of the patients have had unilateral interruption if any is done and these were in the private wards.

These operations have been done almost entirely by the resident staff. There has been no fatality as a result of the venous interruption. There has been only one death from massive embolus following femoral vein interruption. This embolus came from the profunda femoris vein 8 days after the superficial femoral vein had been ligated. Infection has occurred in less than 2 per cent of the wounds. This is amazing when the majority of the operations have been done more or less as an emergency on a previously unprepared field. Complete change of instruments, gloves, and drapes are used on the second side. Lymphorrhea has occurred in a few cases. This complication is reduced to a minimum if the incision is kept parallel to the pulsating femoral artery with as little lateral dissection as possible. Postoperative edema has been variable and in no incidence disabling. It appears that some of the cases are operated upon so early in a true thrombophlebitis and before the classi-

cal picture of full-blown phlegmasia alba dolens develops that the progress of this disease is definitely altered. This probably accounts for the variation in post vein interruption swelling. There has been only one instance of postphlebotic varicose ulcer. The average period of hospital stay after vein interruption has been approximately nine days. When one considers the prolonged invalidism commonly seen in the conservative methods of treatment for thrombophlebitis with the late sequelae of edema, varicosities, and ulcerations, it would seem that early radical treatment represented progress.

Although there has been some difference of opinion in our group concerning the site of phlebotomy and interruption of the veins of the legs and a considerable number of common femoral veins have been ligated, I am definitely of the opinion that the best routine is to open the superficial femoral vein, remove the thrombus if any exist by suction, and then completely divide the vein between ligatures previously placed. It is felt by some that if the profunda femoris is also thrombosed the interruption should be done above this level. Since there are numerous radicals entering the vein just proximal to its major bifurcation, the dissection is tedious and troublesome hemorrhage may occur. Also, it has been pointed out that very serious acute edema of the leg may on occasion result from interruption of the common femoral.<sup>9</sup> We have had only one fatal embolus arising from the profunda femoris after superficial femoral vein occlusion. This, I believe, is a small price to pay for the added safety and ease of procedure when the superficial femoral just below the profunda is selected as the site of interruption.

Inasmuch as we had a definite background of experience with femoral vein interruption for thrombo-embolic disease, it was felt that comparative studies, using dicumarol on similar patients, were indicated. As we have two identical surgical services at the Massachusetts General Hospital, it seemed that these observations might be of value. It was evident from our previous studies that fatal embolism was rare and the morbidity from thrombosis was less in patients under 40 years of age. Also, if infarct or leg signs occur in this age group, proper treatment can nearly always be instituted in plenty of time to prevent catastrophe. For these reasons, no change was made in the handling of this group of patients. In those patients between the ages of 40 and 65 on the East Surgical Service that had no contraindication to the use of dicumarol, prothrombin times were determined and 200 mg. of

the drug administered on the second or third postoperative day. If a definite rise in the plasma prothrombin level did not occur or if the patient could not be mobilized by the time a normal level was reached, a second dose of the same size was to be given. On all patients over 65 years of age who were to undergo operative procedures that prevented early rising, prophylactic femoral vein interruption was practiced. Through the cooperation of L. S. McKittrick (acting chief of the West Surgical Service) the West Surgical patients were used as controls. Pre- and post-operative plasma prothrombin times were obtained on both services in the middle age group.

Doubtless there will be criticism of the small dose of dicumarol used since most reports would indicate that a much larger amount of the drug is necessary to obtain the desired elevation in the prothrombin time. We had had some experience with the variability of its action and had no desire to precipitate serious complications as a result of overdosage. We also knew that the prothrombin time could be elevated in many instances by one, and, if this was not effective, by a second small dose. George Van S. Smith<sup>10</sup> of Boston has used dicumarol in small doses postoperatively in a large group of gynecologic patients and reported informally on his experience. We hoped that we could work out a formula that would make this agent safely available, without the need of so much time consuming laboratory work. It is inevitable that such drugs will be used empirically and already catastrophes have been reported when dicumarol was administered incorrectly and without control.<sup>11</sup> Almost certainly there are many similar but unrecorded episodes.

Contraindications to the use of dicumarol are numerous but obvious. Doubtless many of these are somewhat theoretical, particularly when small doses are used (Table III). Inasmuch as the thrombo-embolic syndrome is not common before the fifth postoperative day, it was expected that these studies might show some regularity in prothrombin time elevation after operation. This was not the case, however, since rarely was there any difference in the pre- and post-operative levels. We were interested to find that approximately 2 per cent of patients in Group II, who had no other contraindication to dicumarol already had an elevated prothrombin time pre-operatively. We considered it unsafe to use dicumarol if the level was over 25 seconds. One patient with an elevation of 26 seconds did receive a dose of 200 mgms of dicumarol,



Table III—CONTRAINDICATIONS TO DICUMAROL THERAPY—Age 40-65

- 
- 
- |    |   |
|----|---|
| 1  | Liver disease including jaundice                                  |
| 2  | Kidney disease  |
| 3  | Diabetes  |
| 4  | Hemorrhagic diathesis, purpura, hemophilia, etc                   |
| 5  | Hyperthyroidism   |
| 6  | Arthritis Patients receiving aspirin                              |
| 7  | Premature arteriosclerosis  |
| 8  | Hypertension, especially patients for splanchnisectomy            |
| 9  | Chest cases   |
| 10 | Patients with plasma prothrombin above 25 seconds                 |
| 11 | Multiple stage operations (planned)                               |
| 12 | Minor surgical procedures and cases suitable for early ambulation |
- 
- 

Table IV

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Of 528 patients admitted to the East Surgical Service from January 1 to September 30, 1945, between the ages of 40-65, 101 received dicumarol. The remaining 427 patients did not receive it for the following reasons

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Hospitalized for minor procedure (includes early ambulatory cases)	48.0%
Admission for study, no operation performed	19.5
Liver disease	6.0
Hypertension	6.0
Chest cases	6.0
Diabetes	3.5
Hyperthyroidism	3.5
Excessive bleeding at operation	3.5
Plasma prothrombin time elevated above 25 seconds	2.5
Arthritis	1.5
Total	100.0%

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in error, without harm. No thrombosis or embolism occurred in these individuals with abnormally high levels but we were not impressed by any certainty of thrombosis in those with abnormally low levels.

From Jan. 1 to Oct. 1, 1945, 101 patients in age group II received dicumarol postoperatively. This represents only 19 per cent of the patients in this Group. The contraindications to its use in the remaining 81 per cent of patients are shown in Table IV, ninety-one patients had only one dose of 200 mgms. and ten had two doses, sixty-two of those receiving one dose had a satisfactory rise of the plasma prothrombin

Table V—POSSIBLE DICUARY COMPLICATIONS

No	Age Sex	Diagnosis	Operation	Dicumarol	Prothrombin Time (secs.)	Complication
1491 L S	60F	Ipsilateral ascending colon	Rt Collec- tomy Ileo- colic anas- tomosis	200 mgm 3 day p o 200 mgm 6 day p o	Pre-op 13 5 days p o 18 8 days p o 21	On 8th p o day developed ecchy- mosis at site of hypodermic in- jections Moderate hemorrhage from anastomosis
178129 R L	47F	Ct Breast	Radical mastectomy	200 mgm 2 day p o	1 day s p o 33	Moderate sanguineous drainage from wound post-operatively
21562 S C	10F	Cystocele Rectocele	Repair	200 mgm 2 day p o 200 mgm 5 day p o	1 day s p o 22 7 days p o 23 9 days p o 25	Some bleeding in catheter 4 days post-operatively
9961 S W	11F	Fibroid Uterus	Hysterectomy Pericor- niaphy	200 mgm 3 day p o	Pre op 21 2 days p o 21 8 days p o 30	Developed small hematoma in wound on 14th post-op day
178674 M B	18F	Cystocele	Cystocele Repair	200 mgm 2 day p o 200 mgm 8 day p o	Pre-op 21 5 days p o 21 9 days p o 32	On 11th day post-op developed infected hematoma at vaginal apex of wound with bloody discharge temperature rose Uterine
192146 A F	50M	Stenosis of duodenal ulcer	Subtotal gastrectomy	200 mgm 2 day p o	5 days p o 20	Patient died suddenly on 10th post-op day Possible cerebrovas- cular accident No embolus at autopsy Permission to examine brain refused

No patient required Vitamin K therapy to combat hypoprothrombinemia  
 Patient #511491 was given a transfusion for hemorrhage from anastomosis

Table VI—THROMBO-EMBOLIC PHENOMENA IN THE DICUMAROL TREATED GROUP

No.	Age Sex	Diagnosis	Operation	Dicumarol	Prothrombin Time (secs.)	Complication
30404 R II	61M	Ca Cecum	Right Colectomy	200 mgm 3 days p o	Pre-op 21 3 days p o 21 6 days p o 22 7 days p o 22	Developed phlebothrombosis 11th day p o. Superficial femoral veins interrupted. X-ray "suggestive of infarct."
35472 F A	49F	Cholecystitis	Cholecystectomy	200 mgm 2 days p o	2 days p o 21 4 days p o 31 6 days p o 19	Developed symptoms of thrombophlebitis on 10th p o day. Superficial femoral veins interrupted. X-ray showed "infarct."
246209 I C	43F	Cholecystitis	Cholecystectomy	200 mgm 2 days p o 200 mgm 8 days p o	Pre-op 21 1 day p o 21 11 days p o 20	Minor episode of calf tenderness. Subsided in a short time. Femoral vein interruption 2 years previously.

time while 29 had little or no measurable response, five of those receiving a second dose had a desirable rise while the other five had none. The highest elevation following one dose was 60 seconds and the highest rise with two doses was 45 seconds. None of these had a hemorrhagic reaction requiring a massive dose of 60 mgms of synthetic vitamin K. One patient had a transfusion following a moderate hemorrhage from the suture line in an ileocolic anastomosis on the eighth postoperative day. It is interesting to note that she had no measurable effect from dicumarol. All of the possible complications of the dicumarol treated group are analyzed in Table V. We are not convinced that any of these undesirable sequelae are due to the effect of dicumarol. Such complications occur in patients of this type when dicumarol has not been used. The patient who died more or less suddenly on the tenth postoperative day might have had a cerebrovascular accident but since permission to examine the brain was refused by the family, we cannot do more than say that no other cause of death was found at autopsy.

The three instances of thrombo-embolic phenomena occurring in the dicumarol treated group are analyzed in Table VI. Two of these patients had no appreciable change in the plasma prothrombin time as a result of dicumarol. One of these had had bilateral femoral vein interruption at a previous admission two years before. One patient had a satisfactory rise to 31 seconds on the fourth postoperative day. All three of these patients were ambulatory for some time before they developed signs of thrombosis or infarct. It is quite probable that repeated small doses or larger amounts of dicumarol would have prevented thrombosis in these patients, particularly in the two who did not have a previous history of thrombosis.

Some patients have received heparin and dicumarol therapy following femoral vein interruption in an attempt to diminish the extension of thrombosis in other veins and thus prevent or diminish further infarcts. Also, a few patients have been given dicumarol in an attempt to shorten the course of thrombophlebitis after femoral vein interruption. None have been treated recently in our clinic for the thrombo-embolic phenomena by anticoagulant drugs alone since in earlier reports we have shown that this method was less satisfactory. The convalescent period is greatly reduced by a concurrent interruption of the chief source of fatal emboli. The combination of methods

Table VII—COMPARATIVE DATA EAST SURGICAL SERVICE USING DICUMAROL IN GROUP II AND PROPHYLACTIC FEMORAL VEIN INTERRUPTION IN GROUP III—WEST SURGICAL PATIENTS USED AS CONTROLS

M G H—Jan 1 to Oct 1, 1945

		<i>I</i> 1-39 yrs	<i>II</i> 40-64 yrs	<i>III</i> 65 yrs	Total
EAST SERVICE (Dicumarol)	Postoperative				
	Phlebitis	4	3	2*	9
	Prophylactic	0	3	50	53
	Admissions	448	528	165	1141
WEST SERVICE (Control)	Postoperative				
	Phlebitis	7	14	11	32
	Prophylactic	0	0	0	0
	Admissions	458	562	177	1197

\* Developed phlebitis requiring vein interruption before prophylactic interruption had been done.

also been found satisfactory by Parsons<sup>13</sup>

In the control Group II, there were fourteen instances of thrombosis requiring femoral vein interruption (Table VII) These patients were comparable in every respect to those in the same age group receiving dicumarol

In Group III, there were fifty patients subjected to prophylactic femoral vein interruption and in none of these did any thrombo-embolic episode occur One patient of sixty-eight with extensive carcinoma of the rectum, widespread metastasis and obstruction, reacted badly to colostomy done under novocaine anesthesia Her plasma prothrombin time was 24 seconds She would have had prophylactic femoral vein interruption if her condition had permitted, on the basis of our outlined management of this age group It did not seem feasible to undertake it and there were no signs of phlebothrombosis She died suddenly on the fourth postoperative day of a massive embolus from the veins of the right leg

In the Control Group III, there were eleven instances of thrombosis and embolism One patient of sixty-eight had a large papillary cyst-adenoma of the ovary removed and was ambulatory on her second postoperative day She presented no signs of phlebothrombosis although she had had a mild febrile course during her first week after admission,

thought to be due to necrosis in her pelvic tumor. Her chart had been normal for 3 days prior to laparotomy. Sudden death occurred on the 4th postoperative day and postmortem examination revealed a massive pulmonary embolus arising from the leg veins. In all the other patients in this group, thrombectomy and femoral vein interruption were successfully carried out after signs of thrombosis or infarct were recognized.

There was one other embolic death on the surgical services in the nine month period covered by this report. A man of 45 was being studied for carcinoma of the lung. No operative procedures had been carried out. No evidence of phlebothrombosis had been noted. On the 9th hospital day, he expired suddenly. Autopsy revealed massive pulmonary embolism, arising from the veins of the right leg, oatcell carcinoma of the lung with metastasis to the liver, pancreas and lymph nodes with perforation of the latter into the esophagus.

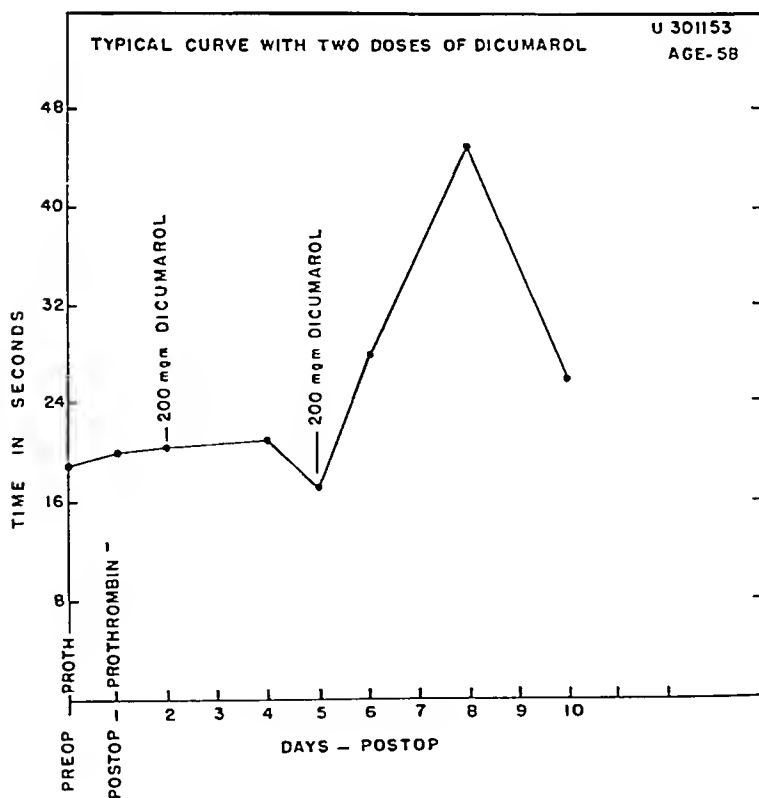
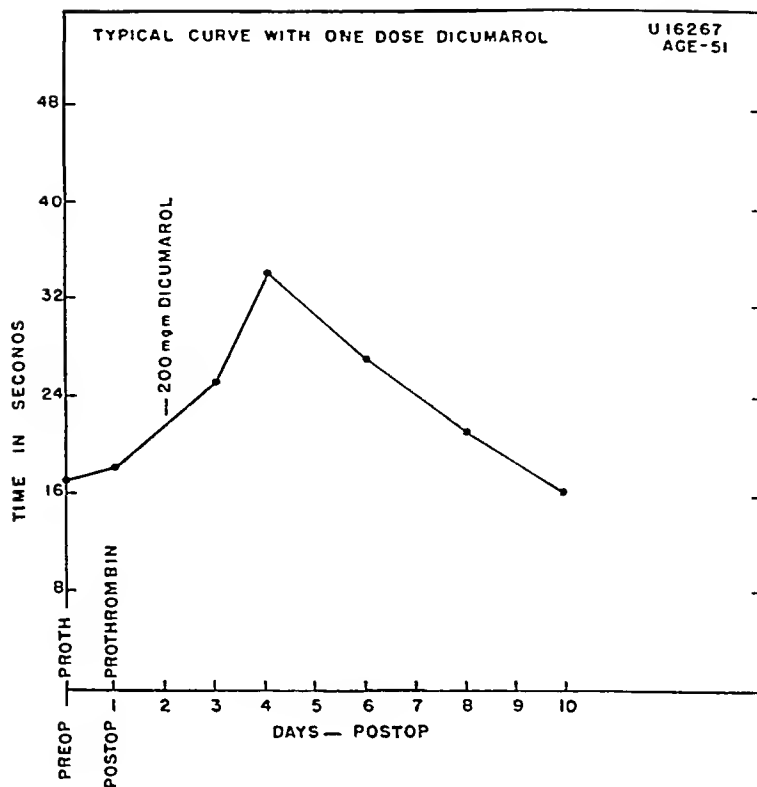
It was felt that we should establish, if possible, the most satisfactory method to our chemists of plasma prothrombin time determinations. Therefore, comparative results were carried out simultaneously on four modifications. The Quick<sup>14</sup> and the Shapiro<sup>15</sup> methods were used both with the undiluted and the diluted serum. Although the variation between the normal and the elevated prothrombin time is exaggerated by the dilute methods and the effect of the drug may be more quickly determined by this modification, there is probably little choice between them. Charts 1, 2, 3, and 4 show the curves obtained during our studies. Our chemists are somewhat inclined to like the undiluted method of Quick better and feel that it gives fewer variations than that of Shapiro. It is obvious that the curves parallel each other with a fair degree of regularity.

This is a time consuming laboratory test and must be done by one of experience. It seems unlikely that any of the present methods could be relied upon unless the technician has been well trained in this specific procedure and did these tests often.

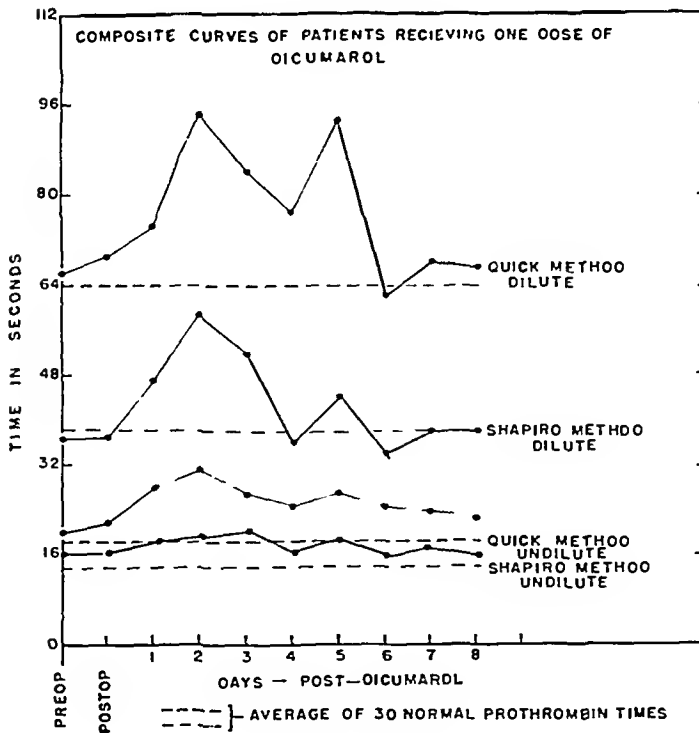
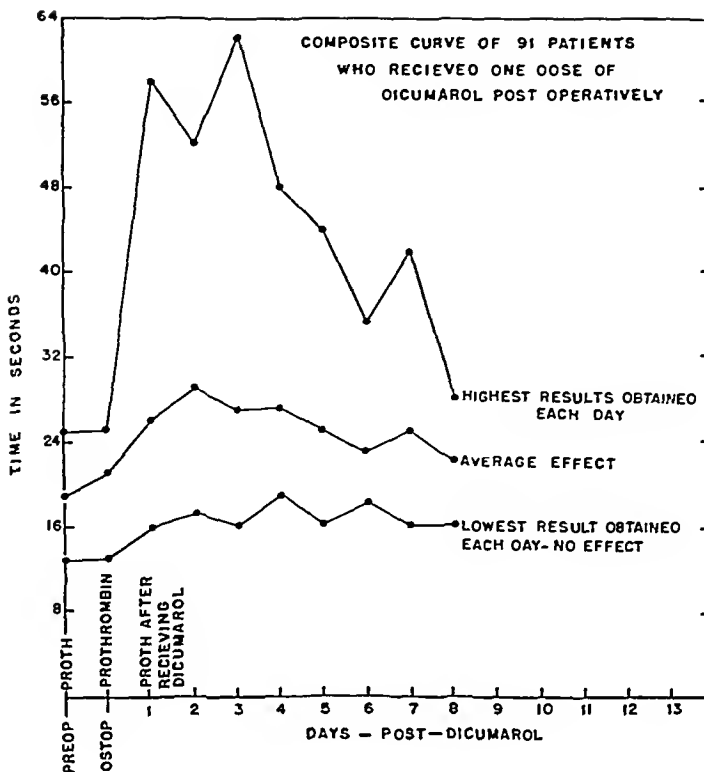
#### SUMMARY AND CONCLUSIONS

1. Thrombectomy and bilateral superficial femoral vein interruption is a safe and satisfactory method of treating early thrombophlebitis. It is a reliable method of preventing pulmonary embolism after signs, symptoms, or clinical chart show evidence of phlebothrombosis.

2. Prophylactic bilateral superficial femoral vein interruption is 1



CHARTS I & II



CHARTS III & IV



safe and harmless procedure and prevents postoperative thrombosis and embolism. It is particularly suitable in the older age group of patients.

3 Common femoral vein interruption is not recommended in spite of one fatal embolus, occurring in our series, from the profunda femoris vein after superficial femoral interruption. Serious sequelae can occur under certain circumstances from common femoral vein occlusion. The technical difficulties far outweigh any added protection to the patient.

4 Dicumarol in small doses appears to be safe and effective in selected patients as a preventive against thrombosis and embolism. It is useful in conjunction with femoral vein interruption after thrombosis occurs.

5 Careful laboratory observations on the plasma prothrombin time preoperatively and after dicumarol administration are imperative for the safety of the patient when this drug is used.

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## SEDATION AS A TECHNIQUE IN PSYCHOTHERAPY\*

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### *Introduction*

 knowledge of the human mind in health and sickness developed, progress toward rational and effective treatment in the field of psychiatry has been associated with fluctuating emphasis on the use of sedation. Although Pinel in France and Tuke in England removed the chains from the insane in 1792, mechanical restraint in the form of strait-jackets and other devices were still used, but as curative instruments rather than as punitive measures. These were soon superseded by another form of restraint induced by drugs and dignified by the term "chemical restraint."

In light of our present knowledge it is probable that these drugs were even more harmful than the physical methods previously employed. Their administration was frequently deputed to ignorant attendants whose main motivation was to keep the patients quiet and their own nights undisturbed. One infamous hospital kept on the wards a black bottle containing a highly concentrated solution. Should any patient cry out or ask for a service, he was forced to take a drink from this bottle, whose salty-tasting contents stimulated thirst, which in turn was satisfied only by another swig, until the patient inevitably became drugged into a stupor in which he no longer bothered his attendants.

In the treatment of the psychoneuroses, sedation has long been used as an aid to psychotherapy. The drugs employed dulled the patients' awareness of their anxieties or decreased their physical symptoms and made them temporarily more susceptible to the influence of reassurance, suggestion and persuasion. By decreasing inner tension, they furthered diurnal rest and nocturnal sleep which were the cardinal objectives of the historically famous "rest cure." Differing only by quantitatively

\* From the AAT Convalescent Hospital (Don Ce Sar), St. Petersburg, Florida. Read October 9, 1945 before the Eighteenth Graduate Fortnight of The New York Academy of Medicine.

greater stupefying effects, the more recent continuous sleep therapy has been and is still being used for catatonic excitement, panic states and even acute war neuroses. These methods "cover up" the patient's anxieties and conflicts with the intent that his internal powers of control and capacities for recovery should be given the opportunity to function. As I shall indicate later, this concept has a limited validity but it indicates that even today sedation is often prescribed for the same reasons as in the past. The patient is quieted and does not bother his physician with complaints that he is incapable of understanding or treating.

In the modern practice of psychiatry the most experienced and skilled therapists use the least amount of sedation. They use it as an adjunctive method, with full knowledge of the pharmacological effect of various drugs on specific functions of the nervous system, to further the influence of dynamic psychotherapy. The technique of sedation has progressed from its role of making the patient quieter, easier to handle and less of a nuisance to the physician, to a sharp tool for the purpose of uncovering the patient's unconscious sources of anxiety and helping him master them.

#### PHARMACOLOGY

Sedatives, hypnotics and anesthetics act on the central nervous system.<sup>1</sup> They enter into easily reversible combinations with the surface membranes of the nerve cells decreasing their capacity for oxygen utilization and hence depress their physiological activity. Minor variations in the chemical structure of the barbiturates alter the effective dose, the speed of action and the duration of effect. Various drugs act on different levels of the central nervous system, probably due to their specific affinity for cells of special chemical constitution (pathoclisis). Bromides and phenobarbital as well as dilantin are cortical depressants probably active on the internuncial neurones of the cortex producing a functional de-afferentation. Most of the barbiturates act first or more intensely on the diencephalon.

The best known sedatives are the bromides. These drugs have a much longer-lasting effect than the barbiturates which are rapidly excreted. Bromides replace the chlorides in the blood plasma and in the red blood cells in a chemical combination which takes time for its disassociation. The quantity of bromide that becomes fixed in the blood

depends on the chloride intake and excretion and the degree of hydration. As a result, the quantity of blood bromide may vary greatly in a patient who is on a constant bromide dosage. He may suddenly develop a bromide intoxication from a change in his chloride balance. Hence, bromides are uncertain drugs and require constant blood bromine determinations to avoid a dangerous quantity above 250 milligrams per cent.

Tatum and Seevers<sup>2</sup> proved by animal experimentation that long-continued administration of barbiturates produces severe disturbance of metabolism and ultimately death. My neuropathological studies of the brains of these experimental animals revealed profound morphological changes due to direct toxic influence of the drug. Suicides from overdoses of barbiturates have furnished sufficient neuropathological material to indicate that the human brain is likewise damaged by the long-continued use of this drug. Therefore, it becomes an important consideration for the physician not to facilitate addiction to sedatives. Habituation to sleep-producing medication is more in the nature of a psychological habit than an addiction. Abstinence from these drugs does not cause severe withdrawal symptoms so characteristic of the morphine addict, but does cause a marked accretion of anxiety and its physiological concomitants. In most states there are laws against the sale of barbiturates to the public without a doctor's prescription. It is the physician himself who is culpable, in most cases, by giving large quantities of the drug and assuring the patient that it will do no harm and is not habit-forming.

Actually, tolerance is established for the barbiturates and larger doses must eventually be prescribed. Those physicians who are content to use the drug as a covering-up technique find themselves not only prescribing increasing quantities but also shifting from one type to another until the wide range of barbiturates marketed under various trade names by a large number of pharmaceutical houses has been exhausted. To avoid this tendency to develop tolerance it is better to stop medication for a few days than to change the medication. Effectiveness of the drug is then rapidly restored.

In order to understand the action of sedatives with specific localized effects it becomes necessary to know something about the hierarchical structure of the central nervous system. This complicated structure has slowly evolved into its present complicated and adaptive functions by

developing new functional structures at its head end (encephalization) Sometimes these new functions are only more adaptive and complicated refinements of older, more primitive functions of lower centers, which they also inhibit.<sup>3</sup> Evolution is thus associated with a continuous increase of long-circuiting of external stimuli higher up the central nervous system. From a rapid and stereotyped simple and unconscious reflex activity of the spinal cord, behavior in man has evolved into a slower, especially adapted cortical function based on experience of past failures or successes.

The reverse of this process, known as devolution, occurs when one of the higher centers is affected by disease. Then the new function is obliterated, evidenced clinically by the loss of certain finer types of performance. But the majority of the symptomatology is of a positive nature in that the diseased center's loss of control over lower structures releases their activity, which may take the form of apparently new and certainly abnormal movements and behavior.

The same effect is achieved when a higher center is put out of control by a drug which paralyzes its function temporarily. A drug which sedates higher functions will produce the same loss of function and release of control over lower centers. Sedative drugs or anesthetics in increasing dosages may knock out the function of the entire nervous system from the cortex all the way down to the spinal cord, eventuating in complete paralysis and death. But by the quantities used in clinical practice two areas of the brain are most frequently affected, sometimes in sequence and sometimes selectively. These are the cerebral cortex and the diencephalon. It is well, therefore, to understand the phasic relationship between these structures.

The diencephalon includes the thalamus, the major nuclear body that receives all sensory impressions derived from outside and within the body. It sends fibers to the hypothalamus which is the diencephalic coordinating center for effector visceral responses. Through its stalk connections with the pituitary body it initiates a slow humoral, and, through its connections with the automatic nervous system, it effects a rapid change in homeostasis, adaptive as response to variations in the external environment. It effects those objective emergency responses which are the somatic correlates of anxiety. It not only sets into action autonomic responses but it also stimulates cortical activity. There is no diencephalic sleep center, to the contrary, it has a driving effect on the

cortex The hypothalamus may be set into action not only by unconscious reflex processes but it may also be called upon by the cortex which perceives the dangerous meaning in the future from impressions received from the special senses But in turn the cortex inhibits the hypothalamus from excessive responses It is this phasic relationship which becomes of the utmost importance for our understanding of the use of sedatives in psychiatry

Small quantities of anxiety in the form of a basic apprehension are economical to the organism, alerting it to external dangers Larger quantities of anxiety and its physiological concomitants are pathological and displeasurable They may arise from weakened control of hypothalamic activity by the normally inhibiting cortex, or from excessive or disturbed activity of the hypothalamus Thirdly, cortical interpretations of external stimuli as dangerous, hence calling for emergency responses, may develop as conditioned reflexes which are no longer necessary and may be non-discriminating To the neurotic more and more of the environment may seem dangerous and an excitation to anxiety and alerting reactions

Sedation or depression of the cortical inhibiting structures releases increased activity of lower structures As an example, ether gradually affects the neuraxis from the cortex down, producing an excitement release stage preceding generalized flaccidity Alcohol is an irregularly descending depressant and only first acts on the cortex releasing previously inhibited behavior In fact, the superego, or internal check on primitive asocial behavior, is facetiously defined as that part of the personality that is soluble in alcohol Both alcohol and ether in small doses produce a state of facile expression and liberation of buried feelings and repressed thoughts, and have been used to effect abreactions These, however, are relatively ineffective because in that stage of depression cortical activity is extinguished and learning is not possible However, it is clear that sedative doses effective in reducing anxiety must be large enough and act fast enough to depress both the cortex and the hypothalamus simultaneously The resulting sleep in exhausted patients may be followed by a resumption of normal cortical control of hypothalamic activity

The barbiturates, for the most part, act on the hypothalamus, at least first, decreasing excessive autonomic activity Alcoholic excitement caused by cortical depression is controlled therapeutically by intra-

venous injections of barbiturates. The same method reduces all psychomotor excitement in panic states or catatonia. By decreasing hypothalamic activity, that structure's bombardment of the cortex is reduced and permanent results may ensue from a breaking up of abnormal closed circles of internuncial neurones.

Finally, the destruction of abnormal conditioned reflexes may be effected by finely graded doses of sedatives which depress both cortex and hypothalamus less than the degree producing sleep. Then the driving force of the lower centers is reduced, cortical reactions to signals of danger are decreased and a new learning process may be endured, thus breaking up the no-longer-economical conditioned reflexes.

### ANXIETY AND INSOMNIA

Psychoneuroses are the result of conflicts between opposing inner psychological forces or between certain drives within man and his restricting, frustrating or punitive environment. At some time or other, such conflicts are signaled to the ego by the feeling of anxiety which is accompanied by physical symptoms manifested by altered functions of the visceral nervous system and by disorders of sleep. Both the subjective and objective components of this reaction differ little from those due to fear of a real external danger, in fact, man often projects the source of his unendurable free anxiety to an apparently rational environmental stimulus.

Anxiety, which is a signal felt by the ego of anticipated danger to its stability by threatened abandonment by external supporting figures, or disapproval by its own ego-ideal, or overwhelming force of its internal drives, is unbearable in free form beyond a minimal alerting quantity. Large quantities are either bound by somatic symptoms or projected to external rationalized fears. But in any case the patient comes to the psychiatrist pleading for relief of insomnia and his direct and indirect manifestations of anxiety. He wants immediate relief and cares not what the cause. In fact, he tries to run away from his symptom, literally and figuratively. Attributing it to a specific environment he will travel, leave his job or change his wife. He will deny its internal source, but refuses to adopt any procedure that will intensify his feelings.

What should the doctor do? Help him run away by manipulating his environment and decreasing his perceptions of anxiety by dosing him with sedatives, in other words, cover up the source of the anxiety, or

uncover the cause and help him master it?

According to our physiological concepts of the organization of the central nervous system, the task in anxiety is either to strengthen the anxiety-controlling mechanisms, the cerebral cortex, to decrease the pressure of the anxiety forces from the diencephalon, or, most logically, to liberate the anxiety in small doses and assist the patient in mastering it through a process of learning

#### CONTINUOUS SEDATION

The continuous use of sedatives for the treatment of neuroses is employed not only by physicians who try to hide the symptoms and anxiety from themselves and their patients, but also by those who have a biologic and deterministic view of the neuroses. Sargant and Slater<sup>2</sup> state that symptomatic treatment is our only aim because we know so little about psychology. They believe that most psychological abnormalities are expressions of unknown constitutional derivatives not susceptible to direct attack. They recommend alcohol for psychopaths, feeling that it makes them lead a happier, more normal better adapted life. They believe in the old James-Lange theory of emotions when they state "We feel fear with our bellies. Abolish this autonomic symptom and we abolish fear."

The majority of chronic anxiety states are little benefited by continuous sedation. Certain exceptions to this dictum include those who have acute flare-ups of anxiety bordering on panic states, or those whose anxieties are forcing them into disastrous motor action or abnormal behavior. In these cases it is often necessary to give large doses of barbiturates by mouth or intravenously, or paraldehyde.

In combat, many men succumb to overwhelming anxiety because their control has diminished by long exposure to cold and wet and long periods of strain without sleep or food. Their cortical control has weakened and a plateau of anxiety has displaced the normal sharp increment and slow fall in response to emergency situations. They are "too tired to sleep" by which is meant an excessive hypothalamic activity uncontrollable by the cortex. For these men, sleep induced by adequate sedation usually rehabilitates their control in a few days. After 5 to 7 days many are able to return to combat. Should anxiety persist beyond this point, processes have crystallized irreversibly which are not stopped by these simple procedures. The neurotic mechanism then requires



definitive psychiatric treatment

Although, for conditions of exhaustion, cortical depressants seem to aid the anxiety-controlling mechanisms to regain strength, there is some evidence that these drugs may be harmful, delaying or preventing learning processes. Watson and Kennard<sup>5</sup> found that the cortical depressants phenobarbital and dilantin delayed the recovery of function following cerebral cortical lesions in experimental animals and neutralized the enhancing effect of Doryl, a cholinergic drug. The sedatives decreased the capacity for cerebral reorganization. It is common clinical experience that bromides and phenobarbital in analeptic doses depress attention and learning, especially in children. Thus continuous sedation, by interfering with the most efficient cortical functioning, may be harmful by decreasing the patient's spontaneous processes of learning and readjustment.

Patients with depression associated with considerable tension manifested by excessive psychomotor activity, usually characterized by pacing up and down, wringing of the hands, and generalized restlessness, may require, in the acute phase, day and night sedation. It has long been noted that barbiturates in themselves have a generally depressing effect on the mood. It is therefore unwise to give a depressed patient a drug which deepens his symptom. It is an old discovery that the only sedative that helps and does not deepen depression when given over a considerable period of time is opium. One-half to three-quarters grain of powdered opium in capsule form three times a day, in combination with sufficient quantity of a laxative such as Cascara to negate the constipating effect of the drug, is a standard symptomatic remedy for depression.

Some patients complain not of the free anxiety but of the stimulating effects of anxiety on both smooth and somatic musculature—producing spasms. Symptoms such as spasm of the colon may be helped by drugs like atropine which are sedative to the sympathetic activity. When anxiety is manifested by spasm of the voluntary musculature in the legs or back, relief may be obtained by the use of neostigmine or prostigmine. Just like hypnotics, these quieting effects are symptomatic rather than etiologic remedies.

There is a common mistake among many physicians that anodynes are good hypnotics. Even if the anxiety manifests itself by pain, such drugs as morphine should not be given. It has no place as an adjunctive for psychotherapy.

## SEDATION FOR INSOMNIA

Patients with anxiety are anxious to get relief from their symptoms and little interested in their cause. They want immediate relief, particularly from the earliest and usually severest symptomatic evidence of anxiety, namely, insomnia. Patients whose anxiety is a signal of an aggressive trend which is rising to the surface usually have a bona fide desire for a sleep-producing drug. However, in them, relief from insomnia is seldom complete and they are usually disappointed in the results obtained from barbiturates.

Passive and dependent individuals whose anxiety is based on the frustration of their regressed needs desire medication of some sort as an indication that the physician is doing all that is possible to help them, and that he recognizes the medical disturbance. Failure to give medication is interpreted to mean the converse, that is, the denial of illness. The patient then feels that the doctor attributes his symptoms to imagination or malingering. It is as if he says "He's not doing anything for me because he thinks I'm putting on, or he doesn't care anything about me."

Although we realize that the source of anxiety has to be uncovered by work on the part of both the patient and the doctor, it is often necessary to convince the patient of his doctor's interest and understanding. The temporary use of a sedative may not only relieve the temporary insomnia but assist in furthering a positive relationship of the patient to his doctor, in other words, a transference relationship.

On the other hand, passive and dependent individuals may persist in requesting sedation even though their psychological state has progressed toward recovery beyond the stage at which such medication is needed. The request then becomes an attention-getting mechanism and the drug has a psychological effect. This impression is gained by the fact that satisfactorily disguised placebos administered under the guise of a sedative are not easily differentiated from the actual drug and seem to have the same effect. Thus it is the fact that a medicine is administered rather than its pharmacological effect that helps the patient gain his sleep.

Patients with severe anxiety usually have a very high tolerance for barbiturates, which may be due to the high level of nervous excitation which requires a larger dose to sedate. On the other hand, there is some evidence that acute anxiety states alter absorption from the stomach and intestinal tract which would therefore delay the effect of drugs adminis-

tered by mouth. As evidence for this phenomenon is the fact that many patients with anxiety have an excessively long "hangover" effect from the use of barbiturates which could be due to a slow absorption.

Self-medication for insomnia in the form of alcohol is quickly adopted by many patients with acute anxiety, and there is no question that in small doses alcohol's depressing effect on the cortex decreases the impact of the anxiety-producing mechanisms. But, unfortunately, alcohol is rarely imbibed in pharmacological doses, and quantities greater than the optimum effect are usually ingested. Many "shell-shocked" veterans of the last war have learned that comfort may be obtained by the use of  $\frac{1}{2}$  grain of phenobarbital in combination with a few bottles of beer. Both the drug and the alcohol are cortical depressants. However, when the alcohol or the phenobarbital has depressed the cortex so much that it not only does not permit the apperception of anxiety stimulated from activity of the lower centers, but also loses its inhibitory effect, anxiety and its effects become accentuated. During this phase they very frequently act out extremely violent abreactions and often become extremely aggressive and perform asocial and often criminal acts. For these people a sedative which acts on the hypothalamus is necessary to reduce the effect of the anxiety-producing mechanism since there is no longer any cortical control of it. Large doses of paraldehyde, or better still, intravenous sodium amytal, are usually necessary to sedate such people.

The anxiety-ridden patient not only has difficulty in getting to sleep but he has trouble maintaining this state for any length of time. The most effective use of barbiturates consists of a combination of a quick-acting and a prolonged-acting drug. For this reason, combinations of seconal and nembutal or amytal or barbital are advisable.<sup>6</sup>

Sedatives that are temporarily given to patients should be accompanied by pertinent instructions as to the meaning of both wakefulness and the sedation. They should be told that sedatives are temporary corrections and that wakefulness is but one aspect of their illness which can only be helped by an understanding of its meaning in terms of past experiences. They are easily led to understand the futility of large covering-up doses by reminding them that acute anxiety breaks through and destroys sleep by bringing up old unmastered memories.

It is a strange habit of pharmacopoeias and compendia of remedies to indicate minimal and usually ineffective doses. Not only are sedatives

of no value in small doses but they are also harmful. A few examples may be given, 1 ½ grains Seconal, in an acute anxiety, is usually ineffective, hence its dose should be doubled. Nembutal is better given in doses of 3 gr. and sodium amytal 3 to 6 gr. Four or five drams of paraldehyde by mouth and 10 cc. of the same drug intramuscularly is most effective. There is no standard dose of sodium amytal by vein. It should be given regardless of the dosage until the physical effect is obtained. Medication has no purpose unless it is given in effective doses. When accidental or self-administered overdoses of barbiturates produce dangerous coma, intravenous picrotoxin or metrazol are good antidotes and should be used in dosages sufficient to arouse the patient.

### CONTINUOUS SLEEP

Continuous sleep is a procedure first developed abroad and then applied in this country to a varied group of agitated psychotics and neurotics with panic. At first it seemed to have some success in the excited catatonics, but gradually enthusiasm for this therapy has diminished. Nevertheless, it was applied to the treatment of acute war neuroses associated with much anxiety. Spiegel and I found it ineffective in reducing anxiety or furthering psychotherapy.<sup>7</sup> Hastings, Wright and Glueck<sup>8</sup> reported excellent results but re-evaluation of their work by later psychiatrists in the same Air Force did not substantiate this enthusiasm. However, even yet certain military psychiatrists use modified continuous sleep and sub-shock doses of insulin. We repeated the continuous sleep treatment on anxious returnees and found that not only was it therapeutically ineffective but it also made the patients worse. Our first 20 patients were all medically discharged from the Army.

I shall not give the details of the technique except to state that 4 out of each 24 hours must be waking hours for the purpose of physical movement, toilet function and feeding. During the rise into awakeness and the sinking into sleep, twice daily, the borderland state is associated with terrifying hypnagogic hallucinations and panic-inducing anxiety. Lasting so long and experienced without the support of the therapist, such episodes seriously weaken the anxiety-controlling mechanisms still further. The uncontrolled delirium becomes destructive.

The human organism frequently adopts a technique reminiscent of the instinctual defensive immobilization of lower animals. Confronted

by external danger, the rabbit or the guinea-pig may not fight or run away but may merge itself, immobile, with the protective coloration of its environment. Men with war neuroses frequently shut out all sounds, sights and memories of the dangerous events by retreating from the anxiety-stimulating conflicts into stupor, deafness, muteness or blindness. In certain civilian neuroses we frequently find that instead of free anxiety and insomnia the patient adopts the defense of hypersomnia and sleeps for much of the day and night. Just like the stupors in combat, such defenses are uneconomical and unadaptive. They should not be imitated by an active therapeutic principle of inducing continuous sleep.

### UNCOVERING TECHNIQUES

Aside from their use to produce continuous sleep and for sedation in states of exhaustion, barbiturates are used in psychiatry for the purpose of facilitating uncovering techniques of treatment. Although the doses utilized are non-toxic and devoid of danger, the psychological effects are not without harm if the procedures are carried out by unskilled physicians who have not been adequately trained in dynamic psychiatry. The quantity of liberated emotion may overpower the patient's weakened anxiety-controlling mechanisms unless the therapist is skilled in assaying the patient's capacities to synthesize and integrate feelings that have been repressed and which will be released under the treatment. Nevertheless, in skilled hands intravenous barbiturates considerably shorten individual psychotherapy when used as a part of the treatment.

Treatment techniques of the uncovering type are especially utilized in neuroses for the purpose of ventilating repressed feelings and ideas which are etiological to the nervous symptoms. Such uncovering during individual psychotherapy is but the first step in the work of mastery of reactions initiated by external stress. Shortacting intravenous barbiturates hasten this process by quickly overcoming resistances, by decreasing the pain felt by the ego in the process of recall and by effecting a release of feelings in small doses.

Repressed painful or traumatic events and the repressed anxieties and hostilities connected with them are not only exposed during the treatment, but accepted by the patient's ego. He then is able to deal with them in a more economical and realistic fashion, giving up the neurotic compromises which have resulted in his symptoms. This is the process

which is called *narcosynthesis*, since under the action of the drug and with the aid of the therapist, the previously repressed or forgotten feelings and memories are synthesized by the ego. If this process has taken place, the degree of recovery will then depend upon the new grouping of forces within the ego.

*Diagnosis* is furthered by the drug enabling the observer to gain a clear view of the intensity of anxiety, the degree of regression, the strength of dependent trends, the superego attitudes and the dynamic relation of all these factors to each other. The knowledge thus gained can be of great advantage to the psychiatrist in relation to further treatment, even in the absence of any clinical gain to the patient. The repressed emotional situation may be clearly exposed and abreacted in the narcotic state without its achieving any synthesis. Since the material in this event is lost when the individual arouses from the effects of the drug and no change has occurred in the relative strengths of the dynamic forces, there is no symptomatic improvement. This is not infrequently the case in patients whose resistances are very strong, or those whose ego depletion is severe. It is also seen in individuals with rigid super-egos in whom there is strong guilt over real or imaginary failure to live up to ego ideals. In the latter case the failure of synthesis as well as the persistence of severe symptoms appears to be related to an unconscious dynamic need for self-punishment. In this context, the treatment is identical with the *narcoanalysis*, long used in psychiatry, in which the benefit results almost entirely from the insight the therapist gains concerning the patient's concealed difficulties. In a similar manner the method may be utilized for diagnostic purposes to determine the progress a patient has made after therapy.

As a means of inducing *narcobypnosis* intravenous barbiturates are successful, but the effect of persuading or forcing the patient to give up his symptoms by strong suggestion is not long-lasting since the basic causes are not exposed. This procedure is not recommended except for purposes of expediency.

The method should not be used in debilitated individuals suffering from cardiac, renal, hepatic or pulmonary disease. It should not be used during the time that the patient has an upper respiratory infection. These drugs are ineffective following prolonged alcoholism so that drinking should be interdicted at least 24 hours before the treatment.

Schizophrenics and manic depressive psychoses that are highly endog-

enous should not be treated by the method because of the danger of precipitating an overt psychosis or making an existing psychotic state worse, and the danger of precipitating suicidal actions. Patients in a near panic with severely weakened egos, especially those suffering from homosexual conflicts close to consciousness, may be worsened by rapid uncovering techniques. Patients with long-standing character neuroses and psychoneuroses existing prior to stress, psychopathic personalities and compulsive-obsessional neuroses and characters are usually not benefited. The method cannot lift the amnesias produced by alcoholism or cerebral concussion.

Favorable cases are young and plastic individuals who have developed neurotic symptoms as a result of external stress and whose predisposition has been mild or minimal, and patients with repressed conflicts producing regressed dependency reactions, depressions, guilt, hostile aggressive reactions and psychosomatic syndromes of recent origin.

For some individuals who are frightened of the treatment, of receiving an injection, or the "needle," or of the deleterious effects of a drug, further reassurances may be necessary. However, once explanations are attempted in order to reassure an apprehensive individual, further questions are stimulated which require further explanations, so that one must be prepared either to say very little about the treatment or else to give a lengthy dissertation on the subject.

In general, it is wisest not to initiate the treatment until some degree of confidence has been established in the therapeutic relationship and some transference attitudes have developed, although this is not always possible or necessary. Hence, the treatment should never be given until one or more psychotherapeutic interviews have been given and the therapist is familiar with his patient's background, his stress and reactions. If the treatments have been in progress in a hospital or some other institution, the easily observed clinical benefits and the lack of harmful or unpleasant reactions will have produced a general acceptance of the procedure, and individual resistance to it will be minimal.

Sodium amytal or sodium pentothal may be used as desired. The latter has the advantage of being quicker acting and shorter lasting, thus enabling the patient to be entirely conscious at termination of the interview and able to return to his ward alone.

The nurse's tray should contain, in addition to the drug, ampoules

of metrazol and nikethamide (coramine) and an airway in case of choking, coughing or cyanosis indicative of edema of the glottis. Fortunately, this hardly ever occurs in the dosage necessary. Apnea, which may occur transiently for a few moments, is almost never sufficiently prolonged to require therapy.

Sodium pentothal is issued in ampoules of 0.5 gram and 1.0 gram and may be administered in either a 2.5 per cent or a 5 per cent solution. The dosage required for a satisfactory narcosis is usually between 0.25 gram and 0.5 gram, though in some very marked anxiety states in large individuals, more than 1.0 gram may be necessary. The individual reclines upon a bed in a semi-darkened room and is told that he is going to receive an injection which will make him sleepy.

The drug is injected into the antecubital vein at a slow rate (0.1 gram per minute), while the patient is asked to count backwards from the number 100. Shortly after the counting becomes confused and before actual sleep is produced, the injection is discontinued, although the needle may be allowed to remain in the vein until it is ascertained that the proper depth of narcosis has been achieved. This may be deceiving. Some individuals suddenly fall asleep in the midst of their counting, only to become wide awake and alert on slight stimulation. In such cases, more of the drug must be injected. If the individual is mute or stuporous and therefore cannot count, a corresponding depth of narcosis must be estimated from the tonus of the eyelids and pupillary reflexes. In rare instances, the injection is difficult because of a violent tremor of the arm. In almost every case, there is some increase in the symptoms of anxiety as the injection is initiated. As it proceeds, however, the tremors subside and the individual becomes quiet. Speech may be somewhat thick and there may be spasmodic coughing but serious pulmonary difficulties with the doses and technique described are rare. Vomiting during or after the injection is rarely seen.

By the time a satisfactory level of narcosis is reached, a few individuals will begin to talk spontaneously. In the greater number of cases, verbal stimulation is necessary. The amount of stimulation which must be given in order to start the individual talking and to bring him into contact with his painful experiences varies tremendously. Some react with the first few words, selecting a crucial stimulus and launch into an account of the experience. Others resist for various periods of time. When such resistance is maintained, the stimulation can be made more



dramatic and realistic

The individual reactions during the progress of the treatment are extremely varied. In some men the situation is relived with such intensity that the activity requires a motor rather than a purely verbal outlet. Others live through the scene verbally and emotionally without much motor activity. The tendency to live through the various combat episodes in the present tense leaves large gaps in what the therapist can grasp of the action, like listening to one end of a telephone conversation. The patient, therefore, is constantly urged to recount the episodes in the past tense, giving a clear picture of what took place. The minuteness and wealth of detail which floods the memory, even for events which took place many months and even years past, is always impressive.

The events which are depicted with the realistic impact of an expert dramatic production are probably always true counterparts of what actually took place, rather than fantasies such as are produced in dreams or hypnotic states. The emotional reactions, however, do not represent necessarily the actual behavior during the original episode, but rather what the patient repressed and controlled in order to carry on.

Some men return over and over again to one short traumatic scene, living it through repeatedly. In such cases, more than one pentothal treatment may be required, each one bringing out new pieces of repressed material as if the ego's tolerance for the painful memories increased in the intervals between each treatment.

During the time that the patient is in a close emotional contact with the traumatic situation, the therapist may play an active or passive role in the performance to the degree required by the process of the abreaction. No attempt should be made to produce an hypnotic situation, nor to direct the material into any definite channels unless there is a clear indication that resistance has developed to the communication of some thought, event, or feeling which was on the point of emerging. In this case, the therapist may encourage or exhort the patient to communicate the painful material. In most instances, if the resistance is still powerful under the influence of the drug, no amount of work on the part of the therapist will be of much avail, although another pentothal treatment at a later time may accomplish the desired result.

The therapist usually remains as a vague background figure, from which vantage point he can step into other roles as it becomes necessary. Many men, especially those with free anxiety, a stable ego organization

and a firm contact with reality, are aware of the psychiatrist's presence throughout the treatment. They talk to him directly, telling their story in the past tense and relying on him only for moderate support and sympathy during moments of strong emotion. Others, in whom there has been more dissociation of feeling and who "live through" their experiences under pentothal with great intensity, need more active support.

The therapist may be called upon to play a variety of roles. If the patient becomes convulsed and blocked with the violence of fear, he must step in as a protective and supporting figure, comforting and reassuring him. When intense grief and anger or guilt are exhibited, a forgiving and supporting attitude is required. At the same time, some steps may be taken here to point out the irrationality of the guilt, although this is usually best left to a later point in the session when the individual is no longer under such strong emotional stimulation.

Some men who talk constantly throughout the session to their friends become blocked at certain points either because of the intensity of the emotion or because they seem to get no response from their friends. The therapist may then play the part of the friend, stepping into the scene in an active role.

The manner in which the therapist handles the abreaction is an index of his psychodynamic knowledge. He must avoid the liberation of quantities of anxiety which will overpower the ego, yet permit sufficient ventilation. He should permit free associations, not interrupting with questions based on his preconceived notion of the repressed material. He must interpret the productions of the patient and not expect them to be entirely and directly revealing.

As the effects of the drug wear off and the depth of narcosis decreases, the patient enters that twilight area in which he is still strongly in contact with painful situations and the feelings aroused by them, and yet is increasingly in contact with his immediate environment, the therapist and the present reality. It is at this point that the therapist begins to play an increasingly active role. His immediate concern is to make sure that the material which has just been abreacted is actually synthesized into consciousness. Because of the short-acting effect of sodium pentothal and the absence of the prolonged period of sleep seen with other drugs, the circumstances are mechanically favorable. Still in some instances where the resistances are too strong a synthesis cannot

be established. In such circumstances, the individual usually snaps out of the narcosis into an alert or partially confused state, but completely amnesic for what he has just been saying. A review of the material may bring it back into memory, in whole or in part. On the other hand, efforts to effect a recall may fail and the individual remain completely blank for the entire experience. Pentothal productions should not be read or played back to the patients. The process of remembering is an important work of the ego. The patient should be seen again the next day or as soon thereafter as possible.

In the majority of instances the transition is smooth and the material is spontaneously synthesized into consciousness. Then, because the dynamic forces at work are at the moment so labile and freshly stirred up, the therapist has an ideal opportunity to effect a modification by active interference. Superego attitudes can be easily influenced at this time in the direction of effecting new identifications.

In those with conversion symptoms or protective phobic reactions in whom the ego has for the first time faced the full intensity of the actual anxiety, the symptoms spontaneously disappear since they have lost their functional purpose. However, the ego is in need of encouragement and support for its new frankness. Although in losing the protection of the symptom the ego must suffer the pain of free anxiety, actually in many instances considerable gratitude and relief is expressed as the individual finds that he can do this without suffering too much or losing too much prestige.

During the abreaction, the pharmacological effect of the drug plus the presence of the therapist has enabled the ego to face the painful situation and express its anxiety. The very act of abreaction reduces the pressure upon the ego so that it can continue frankly to face the painful situation after the effects of the drug have worn off. With the pressure relieved, and aided by the therapist, the ego finds that it is stronger than it had anticipated. For the vicious circle which had perpetuated the neurotic compromise in which the ego was continually weak and incompetent, a "benign" circle is substituted. The ego can afford to look squarely at the situation which it had been unable to master and therefore avoided, in part, at least, and to find a new strength. It is encouraged to find new and more efficient techniques to master the situation or at any rate to control its anxiety.

Pentothal is never the entire treatment but must be followed by

individual psychotherapy and group psychotherapy or group therapy, depending on the available time and personnel. The ventilated material must be synthesized by "working through."

The capacity of the ego to synthesize the material released from repression is not dependent on the patient's ability to verbalize insight or to repeat the material in a conscious state. Progress of the total therapy should therefore be judged on the patient's symptoms, attitudes, feelings and behavior and not on his intellectualization.

#### SUMMARY

Sedation as a technique in psychotherapy is not a simple matter of prescribing a standard dosage of an advertised drug. It requires an adequate understanding of the pharmacology of the sedative, of neurophysiology and of psychodynamics. Sedation is adjunctive therapy and has an important place in its proper role in the total program of treatment. It may help the organism increase its control over anxiety, it may reduce the quantity of the force of anxiety and it may facilitate uncovering processes and subsequent mastery and learning. Sedation should always be employed in a scientific manner for a specific therapeutic purpose and never as a means of quieting the patient and thus making him less disturbing to his doctor.

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## INFECTIOUS HEPATITIS\*

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INFECTIOUS HEPATITIS has a special interest for us today because it may well come to be designated as one of *the* diseases of World War II, in somewhat the same manner as pandemic influenza became one of *the* diseases of World War I. Both influenza and epidemic jaundice have been known for centuries, but it would be an understatement to say that they were the source of much *new* and unexpected trouble in World Wars I, and II, respectively. The story is also worth re-viewing because it now seems so strange that a disease so common in many parts of the world and so important, should have remained so poorly defined and so poorly understood for so long—particularly in this country. The picture is still not perfectly clear, but the fact emerges now that infectious hepatitis has been masquerading under a variety of names of which at least four can be listed as — 1) catarrhal jaundice, 2) acute yellow atrophy of the liver, 3) Weil's disease, and 4) serum jaundice.

Before attempting to say how much or how little of these four conditions are actually included under the term infectious hepatitis it may be wise to give a brief clinical picture of this disease so that it may be clearer what we are discussing. Primarily the term *infectious hepatitis* refers here to the same disease which the British call *infective hepatitis*, and others call *epidemic jaundice*. As the name indicates it is an infectious disease. It appears either sporadically or in large or small epidemics. Family outbreaks are traditional with the disease appearing first in one member and then about a month later, in other members. Early symptoms point to a disturbance in the upper gastrointestinal tract, evi-

\* For much of the material used in this lecture I am indebted to Major W. P. Havens, Jr., M.C., Director of the Hepatitis Laboratory of the Neurotropic Virus Disease Commission, U. S. Army Epidemiological Board, Preventive Medicine Service, Office of The Surgeon General and to other members of the Hepatitis Study Group also of the above Board. Information has also been obtained from the reports compiled by Col. M. H. Barker, M.C. and his colleagues in the North African and Mediterranean Theatres of Operations of the U. S. Army in 1942-1945.

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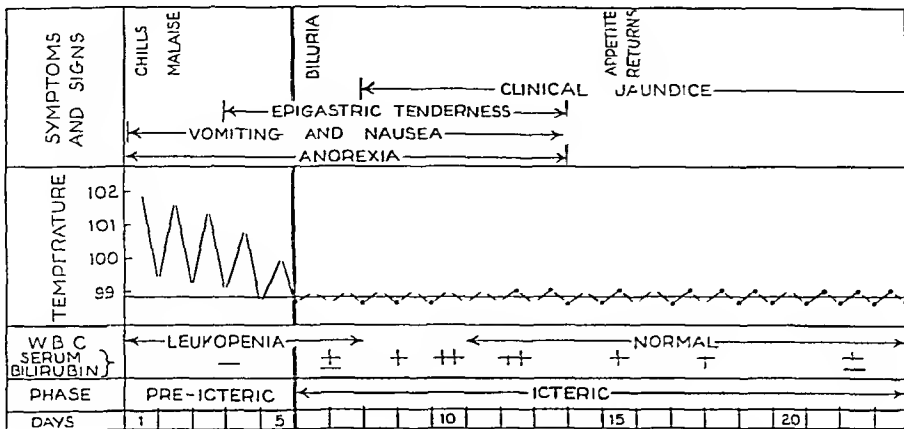


Fig 1 Schematic diagram illustrating the clinical course of an average case of infectious hepatitis in an adult

dences of liver damage occur later. Clinically the picture is similar to that of catarrhal jaundice with a rather sharp division into two phases, *pre-icteric* and *icteric*, see Fig 1. These two phases have characteristic symptoms and signs. The *pre-icteric* stage, which may last from five to ten days, is usually marked by anorexia, nausea, fever, and abdominal distress. The white blood count often shows a leukopenia to be followed by an increase in abnormal lymphocytes, and in this and other respects infectious hepatitis has certain features in common with infectious mononucleosis. The liver is seldom large in this stage but there may be splenic and cervical lymph gland enlargement. The *icteric* stage, which follows, may last from two to ten weeks. Jaundice is usual, but in spite of the name, clinical jaundice is not an essential part of the picture, milder cases do not show it. Usual symptoms in the *icteric* stage consist of abdominal discomfort, in the form of epigastric or right upper quadrant pain, continued nausea, enlargement and tenderness of the liver and light or even clay colored stools. Before improvement starts there is apt to be a good deal of weight loss. The white blood count is normal in this stage.

The prognosis is good, for the disease is seldom fatal—about 2 per 1000 in adults. In many of those cases which are fatal, extensive and diffuse destruction of the liver is found—the picture of acute yellow atrophy of the liver. Fig 2.

But it is not my purpose to give a text-book picture of this disease

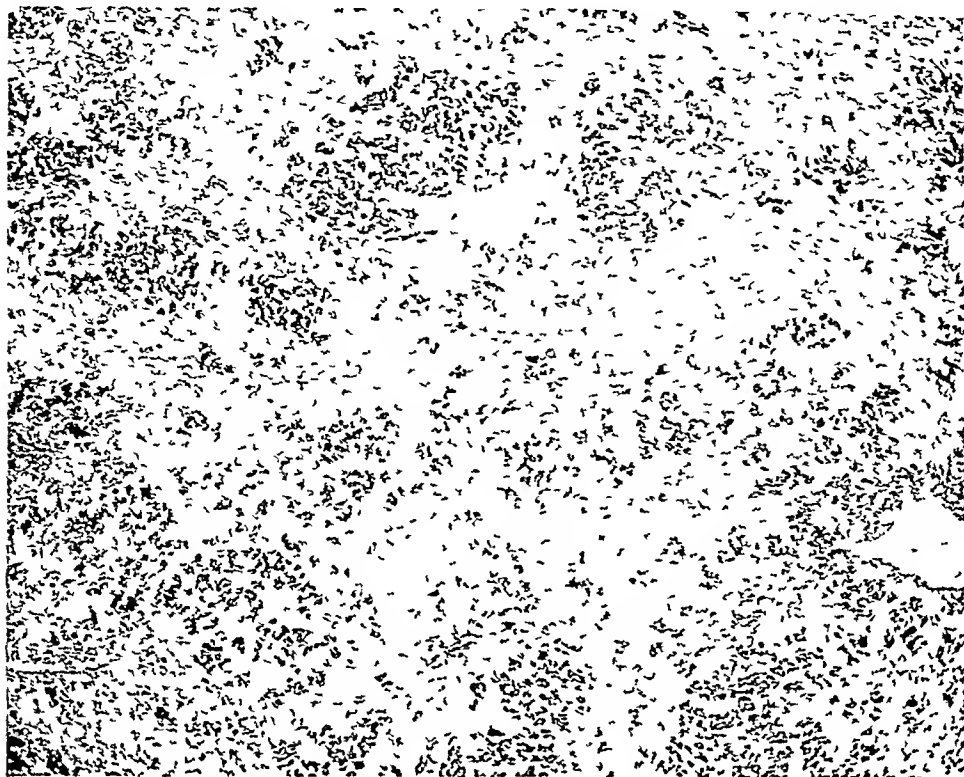


Fig 2 Photomicrograph (low power) of the liver from a fatal case of infectious hepatitis in which death occurred on the 9th day of disease. Great destruction of parenchymal cells is evident. Grossly the picture was that of acute yellow atrophy. (From the Neurotropic Virus Disease Commission, Army Epidemiological Board)

in this lecture.\* Instead I propose to review its history up to the onset of World War II, and then to pick it up again after this point, for it would seem that almost as much history has been written about infectious hepatitis since 1940, as was done in the entire preceding era. Certainly the war has been responsible for much of the recent impetus given to the investigation of this disease.

In my *historical* review I will pick up the threads from various sources and will draw heavily on the work of Cockayne, a British physician who published a review in 1912,<sup>o</sup> under the provocative title, "Catarrhal Jaundice, Epidemic Jaundice and its Relation to Acute Yellow Atrophy of the Liver." That the three conditions mentioned in his title may under certain circumstances represent one and the same disease is also the central theme of this talk.

\* For further and more detailed descriptions of infectious hepatitis the reader is referred to articles by Havens<sup>1</sup> or by Barker *et al*.<sup>2</sup>

Of this triad, catarrhal jaundice has the oldest history. It appears to have been well known to Greek and Roman writers. It attained the dignity of a clinical entity early, and is still regarded by some as a "respectable" disease. Its main attributes were that it was sporadic in distribution, and probably non-contagious. Its clinical course lasted from 3 to 6 weeks, and it was non-fatal. If these laws were broken the tendency was to change the name, *i e*, if multiple cases occurred, catarrhal jaundice became epidemic jaundice, if the clinical course was a short one, it might be called bilious influenza, or if long, bilious typhoid, or if fatal, it became toxic hepatitis or acute yellow atrophy of the liver.

The pathology of catarrhal jaundice has been based correctly enough on the concept of duodenitis as the primary lesion. But there also was a conviction that, as the name rather suggests, the jaundice was obstructive and due to a "plug of mucus" to be found in the common duct at the ampulla of Vater.\* First hand accounts of this plug are few because patients seldom die with the diagnosis of catarrhal jaundice and the pathologist was fortunate indeed to have the privilege of examining at necropsy a fatal case of this disease.

The master pathologist, Virchow, had seen such a case in 1865, with a mucous plug in the terminal portion of the common bile duct. A few others have reported similar observations and this has convinced some in the belief "that cases of true catarrhal jaundice may occur either as a result of a primary ascending cholangitis or following inflammatory changes in structures such as the pancreas and lymph nodes in close relation to the bile ducts."<sup>4</sup>

An opposite view of catarrhal jaundice has long been held by many supporters who believed the jaundice to be due to a hepatitis following systemic infection rather than to the plugging of the bile ducts. According to Rich,<sup>5</sup> in the records of the 11,500 autopsies performed at the Johns Hopkins Hospital during 40 years, there is not a single case in which the diagnosis of catarrhal jaundice could be regarded as accurate. He says, "whatever may be the exact pathogenesis of this condition (which, indeed, probably represents a *mélange* of types of benign icterus of different etiologies), the clinical laboratory findings are unmistakably those of regurgitation jaundice"—as opposed to retention jaundice. So actually the general classification of catarrhal jaundice becomes essentially a clinical concept of unknown etiology and some-

\* For a discussion of literature dealing with historical aspects of catarrhal jaundice and infectious hepatitis the reader is also referred to the article by Findlay, MacCallum and Murgatroyd.<sup>4</sup>



what unsatisfactory pathology as far as the liver is concerned

Another disease in Cockayne's triad was *acute yellow atrophy of the liver*. This has a long history too, supposedly going back to Ballonius, that early French physician who is also credited with the first description of rheumatic fever. The cumbersome term, acute yellow atrophy, to which the adjective *idiopathic* should also be added, fails to indicate much as to the nature of the disease or its etiology and there the situation has remained for many years. Admittedly an anatomical term, it is loosely given to those cases in which some unknown agent suddenly produces widespread destruction of liver cells. It is again a mixture of types of liver injury due to a variety of causes including "catarrhal jaundice," infectious hepatitis and chemical poisoning as well.

But we come to a more definite group of diseases when we begin to examine *infectious hepatitis*, or *epidemic jaundice* or *icterus epidemicus*. The earliest records of this group may also go back to Hippocrates but undoubted reference was made much later and comes from Europe in the mid 18th century.<sup>3</sup> From that time forward many outbreaks are recorded. The disease has a particularly long military history<sup>6</sup> for it was an old and ugly camp follower. It was common in America among the Federal troops in the Civil War. It has been common in many subsequent wars, notably World War I.

By the late 19th century it became apparent that there were at least two varieties of epidemic jaundice—the mild and the severe. The severe form was differentiated by Weil in Germany in 1886,<sup>7</sup> who described the disease which goes under his name. It can be readily differentiated from infectious hepatitis, as a serious infection with a high mortality. The rat has been incriminated as an important vector in its spread. The discovery of its spirochaetal etiology by Japanese workers,<sup>8</sup> in 1914 seemed to fascinate students of epidemic jaundice at that time. It may have so transfixed Dr. Noguchi that he announced shortly his belief that yellow fever was due to a leptospira. In any event the influence of this discovery was such that the term *infectious hepatitis* became for the time being synonymous with Weil's disease, and for a period of about 25 years most of the important American text-books (during the 1920's and '30's) eliminated from their lists the term infectious hepatitis as the name of a disease *per se*, embracing it instead under the title of Weil's disease. Perhaps this confusion may be attributed in part to the fact that there are erroneous reports during this period of finding the

spirochete (*Leptospira icterohaemorrhagiae*) in the blood in clinical cases. Today we realize that many laboratory workers have been led astray by the finding of artifacts in the blood, which bear an uncanny resemblance to a living spirochete.<sup>9</sup> A differentiation between Weil's disease and infectious hepatitis is important because of the discrepancy in prevalence between these two types of liver diseases. To date in the State of Connecticut, for instance, Weil's disease is a great rarity,<sup>10</sup> whereas hundreds of cases of infectious hepatitis may be seen in a single winter. Differentiating features are that there is a leukocytosis in Weil's disease while in infectious hepatitis the blood count tends to remain unchanged, except in the early period when there is a leukopenia. Furthermore the diagnosis in Weil's disease may be established in the early stage by guinea pig inoculation, and in convalescence by appropriate serological tests.

Still another development which tended, perhaps, to confuse the picture of infectious hepatitis during World War I and for a short time thereafter was, that as early as 1864 it had been described as the bilious form of typhoid fever (*typhus biliosus*),—and again as the bilious form of influenza, suggesting a *state of jaundice* rather than a clinical entity. The linkage to typhoid or paratyphoid fever and dysentery came from the fact that epidemic jaundice often occurred under conditions in which enteric infections were prevalent. This notion was strengthened during the World War I campaign in the Dardanelles in 1916, when French medical officers observed a military epidemic of typhoid fever turn into an epidemic of jaundice, in fact become, the "bilious form of typhoid."<sup>11</sup> Bacteria of the paratyphoid group were detected in the blood of these jaundiced patients in this epidemic as were also their specific antibodies. It was suggested at that time that such atypical strains of the paratyphoid group or salmonella (usually *Sal. schottmuelleri*) had acquired *new* characteristics, taking on an "icterogenic capacity." These findings were eventually discounted but they should not be forgotten. They have in fact, been justified in the new light of an important discovery in which salmonellae were recently isolated from the blood stream in two human experimental cases of hepatitis induced by the virus.<sup>12</sup> The men who volunteered for this experiment lived in an institution where salmonellosis was frequent. The bacteremia in these cases has been regarded therefore as an example of *secondary* infection. As such the etiologic aspect of these salmonellae may perhaps be viewed in the same light as we

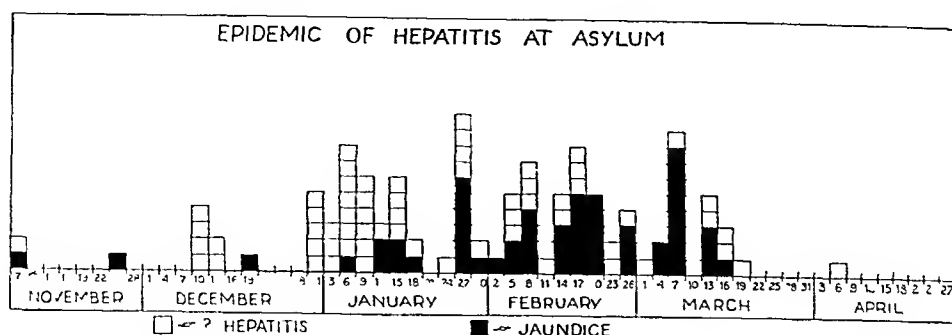


Fig 3 An institutional outbreak of infectious hepatitis in which both patients with clinical jaundice and questionable hepatitis (without clinical jaundice) have been charted. Each square represents one case. (From Havens and Paul<sup>10</sup>)

might view influenza bacilli in a case of influenza A or B.

A linkage with influenza is also understandable today. There are many cases of infectious hepatitis in which jaundice never becomes apparent. They may even be so common in some epidemics that the ratio of icteric to non-icteric cases may reach 1:1 or even more. See Fig 3. The symptoms of these non-icteric cases are not very definite but include fever, malaise, and vomiting. Such cases might have been easily confused with influenza, particularly if the loose term of "intestinal gripe" is employed. When they are frequent in any particular outbreak it is not hard to see how the concept of the bilious form of influenza could become popular.<sup>13</sup>

This then was the rather confused state in which infectious hepatitis was viewed during the 1920's. Blumer<sup>14</sup> was among the first in this country in that period to uphold the identity of infectious hepatitis and to point out that it was common. He believed catarrhal jaundice to be the sporadic form of infectious hepatitis. Only recently have these views been widely accepted, and substantiated by a growing number of reports from England,<sup>15</sup> Europe<sup>16</sup> and this country, notably by Molner and Meyer in Detroit.<sup>17</sup> The latter described large epidemics of jaundice, obviously *not* due to the spirochete of Weil's disease. Proof of this lay in the fact that *serological* tests for Weil's disease had by that time come into being, and negative serological reports had been found in a great majority of their cases of infectious hepatitis, some of which prior to the use of this diagnostic test, might have been classified as Weil's disease.

This brings us to World War II—a landmark in the history of infectious hepatitis. Our first contact in this second chapter began shortly after the United States had entered the war, when the U. S. Army was

suddenly confronted, early in 1942, with a large outbreak of jaundice of unknown type. This new variety of jaundice did not remain unidentified for long, however, but was soon recognized as *homologous serum jaundice*,<sup>18</sup> described by Findlay and MacCallum<sup>19</sup> in 1937, and others<sup>20</sup> later but still relatively unfamiliar in 1942. Serum jaundice is an artificial disease readily spread as the result of transfer of the causative virus from one individual to another when infective blood happens to be drawn for use in transfusions, or as immune sera, or as in this instance, as a stabilizing agent for the preservation of yellow fever vaccine. This virus is similar but not identical to that of infectious hepatitis and the same might be said of the clinical picture. The two diseases appear to be cousins. It is also likely that some examples of "serum jaundice" actually represent the artificial transmission of infectious hepatitis, although one cannot say that all serum jaundice belongs in this category. The agents of both diseases besides being filterable are both resistant to heat at 56°C, both fail to infect any known laboratory animals and yet both give rise to jaundice in humans when inoculated parenterally. But in *infectious jaundice* there is usually a relatively short (25 days) incubation period, and in *serum jaundice* it is longer—60 to 150 days or more. An attack of serum jaundice does not produce immunity against infectious hepatitis. Moreover, there is another difference between the two, experimentally at least, in that an attempt to recover virus mid-way through the short incubation period of a subject experimentally infected with infectious hepatitis was unsuccessful—whereas during the much longer incubation period of serum jaundice, virus is apparently circulating in the blood for weeks. In one instance it was found 60 days prior to the onset of jaundice.<sup>21</sup> This means that in apparently healthy individuals there are long periods in which the blood is infective. These pre-illness carriers are of some danger to the community if they happen to be donors of blood or if they happen to be attending a clinic where immunization procedures are being casually used. The patient with active infectious hepatitis is not so dangerous, because of the fact that he is apt to be sick during his infective period and his symptoms alone would be enough to warn any physician not to use his blood for the various purposes for which blood is used today. The importance of this rests on the fact that numerous examples of serum jaundice have resulted from transfusions, from the prophylactic injection of serum for measles for mumps, and other virus diseases, and apparently from the use of im-

properly sterilized syringes<sup>22</sup> Serum jaundice therefore may be a variant form of infectious hepatitis about which we have learned by the hard way. But unfortunate as this experience may have been, it helped pave the way to the concept of using man as an experimental animal in a disease in which no laboratory animal was available. The use of human volunteers has in fact greatly increased knowledge of both serum jaundice and infectious hepatitis during recent years.

This brings us back to infectious hepatitis, to 1940, and the recent war. And it brings us back to the real problem with infectious hepatitis in this war, which was its unexpected prevalence in certain military zones. The disease was and is common enough in Europe and elsewhere, but it was in the Mediterranean area that its full import as a military disease was first encountered. Here in 1941, and the three subsequent winters there were many thousands of cases in British<sup>23</sup> and American<sup>24, 25</sup> troops. There is no good reason to believe that this disease was different from that seen elsewhere but it seemed to flourish better in the Middle East and the Mediterranean littoral, as it had in 1916. The disease was thought at that time (1940-43) to be spread by droplet infection although this view was not universally accepted. Actually this question of the mode of spread was of fundamental military importance, needing settlement at the earliest opportunity, for knowledge of the mode of spread of infectious hepatitis is the basis on which the whole program of prevention sometimes hinges.

It was in this part of the world, namely Egypt,<sup>1</sup> North Africa,<sup>24</sup> Sicily and Italy<sup>2</sup> where the disease was particularly prevalent among American troops. And it was also there that some of the investigative work on infectious hepatitis was started. For these investigations preliminary information derived from British military experience in the Middle East was invaluable to us. The work of van Rooyen and Gordon,<sup>26</sup> and Cameron<sup>27</sup> was particularly helpful. It is a tribute also to the Medical Department of the American Army in general and the Preventive Medicine Service in the Surgeon General's Office in particular, that they had the foresight to assign small teams of research workers to survey this problem in the field. It is fortunate also that the Medical Department in the North African and Mediterranean Theatres of operations in 1943-45 was able to assign a number of very capable medical officers to this problem in Italy, and some of their reports<sup>2, 25</sup> are now available to us. And finally it is appropriate to mention the part played

by many volunteers who offered themselves as subjects for these studies

As a result of these Army investigations, the following facts some of them new, and others old but better clarified, were established. The disease has been repeatedly reproduced in humans by the injection or the feeding of the etiologic agent—now considered a virus. This virus has not been “isolated” in the sense that it has been seen or cultured or transmittted to laboratory animals, for repeated attempts in rodents and all sorts of monkeys and even chimpanzees<sup>25</sup> have been negative. But many of its properties have been established by using man as the experimental animal. It can be passed, for instance, serially in man<sup>29</sup>. It is filterable and it is quite resistant, withstanding heat at 56° c for one half hour,<sup>29</sup> as well as chlorination viz. one part chlorine residual per million—Neeffe, *et al*<sup>30</sup>. It has been presumably found in drinking water<sup>31</sup>.

Among original claims of success at human transmission are those of Voegt in Germany, published in 1942.<sup>32</sup> Details are incomplete but Voegt described having infected a few volunteers by feeding them duodenal fluid, urine and blood. British studies were carried out in Palestine by Cameron<sup>27</sup> a year later when serum and whole blood from cases of hepatitis were injected intramuscularly into six British soldiers. A number of cases of jaundice were produced after an irregular incubation period.

A year later experiments were reported in England in a short note by MacCallum and Bradley<sup>33</sup> who found the virus in feces and found that the disease could be induced in arthritics who volunteered for these experiments by feeding this material. These results were independently duplicated and enhanced by Havens and his associates, in the Army Laboratories of the Neurotropic Virus Commission established first in Cairo, Egypt, and later in this country at the Yale University School of Medicine,<sup>34</sup> and again later by Neeffe, Stokes and Reinhold<sup>3</sup> of the Commission on Measles and Mumps at the University of Pennsylvania Medical School. The strain used by Havens was collected from a soldier taken ill while in action in Italy and with this strain of infectious hepatitis virus it was found that this disease could be readily produced experimentally in man by the oral route, that is, by feeding the infective feces or spraying such material into the nasopharyngeal passages. Similarly infectious hepatitis could be produced by feeding infective serum as well as by its parenteral administration. In both instances the incubation period ranged from twenty to thirty days and infection was

induced in from 60 to 66 per cent of those tested. It was also shown in subsequent experiments that it was in the acute active stage of the disease when the virus could be detected in the blood and feces, and not in the incubation period or the convalescent period<sup>35 36</sup>. To date experiments in this country which have attempted to demonstrate the virus in the nasopharyngeal washings and the urine have been negative<sup>36</sup>.

The evidence from experimental observations is strong that the intestinal-oral circuit is therefore one of the natural routes of spread of this disease and this, coupled with the field observations that this disease flourishes where camp sanitation is bad,<sup>37</sup> and that water borne infections have been described,<sup>31, 38</sup> is presumptive evidence that this infection should be regarded as a member of the enteric group until proven otherwise.

And finally and perhaps the most useful of discoveries in connection with the disease which has also been made by members of an Army Commission, was the discovery by Stokes and Neefe<sup>39</sup> that this disease could be prevented as in measles, by the injection, during the incubation period, of gamma globulin. In view of the long incubation period, presumably covering twenty-five days, infectious hepatitis is a disease which lends itself rather well to this type of passive immunization.<sup>40</sup> This allows for a period of about seventeen days after exposure during which the inoculation can be effective. If given within six days of the onset there is less chance of preventing an attack of the disease than if given immediately earlier. This discovery is in keeping with the idea that immune bodies develop in the disease as an expression of an immunity which is probably lasting.<sup>41</sup>

In summary therefore, we find that as a result of work largely carried out during the past few years the disease, *infectious hepatitis* stands on much firmer ground than it did before. The accumulation of new information has led to the identification of the causative agent as a filterable agent, to the clarification of its clinical picture, to its assignment as a member of the group of enteric infections, and to its prevention by passive immunization. From a nosological point of view it would now seem as if the term catarrhal jaundice could be eliminated from clinical literature, unless it can be shown to serve a more useful purpose than is apparent to us now. Furthermore, there is now less reason than ever to confuse infectious hepatitis with Weil's disease. As to serum jaundice and infectious hepatitis, these two seem to have much in com-

mon and it is well to keep this relationship in mind, if only for the reason that both may be artificially and inadvertently produced by transferring blood or serum from an infected to a well individual and this may even result from the use of improperly sterilized syringes

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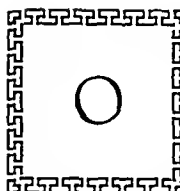
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# THE EYE AS A GUIDE TO LATENT NUTRITIONAL DEFICIENCY DISEASES\*

*A Clinical Study of Ocular Diseases at an Advanced Base Hospital in the Southwest Pacific*

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 OCULAR manifestations may be the first signs in systemic disease, or they may appear associated with other symptoms. In either instance the eye lesions often will suggest or decide the diagnosis. Occasionally a widespread disorder, such as arteriosclerosis, is recognized exclusively by the eye signs. These facts apply equally well to generalized pathologic conditions, viz., infections, metabolic disturbances and vitamin deficiencies.

Having already made experimental observations on changes in the eye secondary to vitamin deficiencies, I became interested in determining whether similar ocular lesions were present in a group of service men suffering from malnutrition. Among the Marine and Naval personnel with various eye complaints who during the past year had been examined in the ophthalmic department of an advanced base hospital in the Southwest Pacific, many had subsisted on a restricted diet. While no individual records are available, still the basic findings are sufficiently definite to permit certain conclusions.

The majority of these men had been in the actual front lines for periods of more than six months, they were recent evacuees from Guadalcanal, New Georgia, Bougainville and other islands of the Solomon chain. Canned food had been used almost exclusively, and deficiency in several essential elements, among them vitamins and minerals, was unavoidable. This study is concerned with the eye conditions of men who had been on a limited fare for six to eighteen months.

Whenever any of these patients complained that his sight had been impaired, his visual acuity was tested and then compared with the

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corresponding data in his health record at the time of enlistment. For enrollment of these pre-Pearl Harbor men a minimum reading of 15/20 in each eye had been required. It was now found that the eyesight in a few of this group had been reduced to a marked degree.

The acuity of some eyes was 6/20 or even 5/20 with the fellow eye reading 8/20 to 12/20. It is conceivable that isolated patients might have memorized the chart for the initial visual test registered in their records but the fact that all of these patients had noticed a real impairment in vision, and the fact that a large number of them showed the same symptom after all had been in similar circumstances, justify the findings.

In this series of service men poor sight was the major eye complaint. With the use of 6 drops of a 4 per cent solution of homatropine, one drop instilled in each eye at 10 minute intervals, and by refracting the eyes after the lapse of 20 minutes following the last drop, it was discovered that these men were myopic, both by retinoscopy and acceptance. To give them 20/20 vision, or better, a minus 2.5 to a minus 1.25 diopter lens was accepted. No abnormality of the crystalline lenses could be detected.

The apparent onset of this *actual myopia*, or the aggravation of a trivial degree of near-sightedness, in these nutritionally deficient men is additional evidence in support of earlier animal and human investigations made by the author.<sup>1</sup> Over 50 per cent of the patients with progressive myopia in these studies revealed either a reduction in the myopia or a stationary condition after the administration of vitamin D and calcium. Approximately 33 per cent had less myopia. In some individuals an actual shrinkage of the myopic eyeball had taken place.

It should be remembered that a moderate percentage of myopic persons will suffer from *night-blindness* along with short-sightedness. The indicated therapy for myopia,<sup>2</sup> however, may also improve the poor night-sight.

Another symptom for which a number of Navy men sought relief was "inflamed eyes." There were those who had attacks of redness of the eyes, accompanied by the annoying symptoms of itching and/or photophobia. Frequently they complained that local therapy was of no avail. Such remedies sometimes aggravated the condition. Examination disclosed the varied signs of *vernal catarrh*, but a definite diagnosis never was made unless a pathognomonic stringy discharge could be recovered. Every case seen was of the mild type. It was unusual for any patient

to state that he had suffered from similar complaints before being ordered to his current duty. It must be admitted, nonetheless, that this catarrh may have been present in some men prior to enlistment, in view of the fact that allergic conjunctivitis is so prevalent in its asymptomatic form. Still, in these patients it can be logically assumed that the vernal catarrh was not sufficiently advanced to produce symptoms until the nutritional disturbance was intensified after departure from the States. The belief that allergic conjunctivitis has a nutritional basis is not new, for observations previously published<sup>3</sup> established this fact. Almost every patient in this former study was benefited appreciably by the use of vitamin D and calcium in sufficient dosages.

Earlier investigators have shown that myopia, night-blindness and vernal catarrh are related entities. This being so, it is not surprising that the same therapy is of value in all of these conditions.

Of the service men who had varied ocular complaints, several were found to have slightly *hazy fundi oculi*. In this group neither vitreous or lens opacities, nor corneal or fundus disease could be demonstrated. Further examination revealed the disc with a mildly blurred margin and often with a thin peripheral rim of pallor, though rarely with a diffuse pale pink color. It was found that physiologic blind spots and central form and color vision in many of these men were normal, yet optic nerves showing such signs could not be considered healthy. The dividing line between the normal and the abnormal is always controversial. In no wise did the fundi oculi in these patients resemble those of normal persons as seen in the States, where adequate nutrition is not so difficult a problem. The hazy fundus oculi and pallor of the disc may be manifestations of a latent deficiency state, since in earlier research we found comparable lesions had developed in animals on depleted diets. These experimental ocular signs were then considered as part evidence of the deficiency.

A fair percentage of the service patients with *pallor of the optic nerve* had enlarged blind spots. In others with enlarged blind spots ophthalmoscopy revealed completely normal fundi. These two latter groups almost invariably showed signs of malaria or a focus of infection or both during this period of malnutrition. Seldom was excessive smoking and/or drinking discovered to be a cause. It was unusual to find that this *retrobulbar neuritis* was a leading symptom of multiple sclerosis. Except in the cases of multiple sclerosis, all of the other patients with

retrobulbar neuritis were cured by the specific treatment of the infection or infections brought out by thorough examination. The criteria for cure were the presence of normal blind spots, normal central form and color vision, and normal optic discs. No one whose condition was diagnosed as retrobulbar neuritis was evacuated to the United States. Complete recovery usually followed the elimination of foci of infection and/or other corrective measures, during which course of treatment nutritious food was served. It was then impossible to judge the precise factor or factors concerned in the cure—whether restoration of the optic nerve to normal was due to the disappearance of the infection or toxin, the improved nutrition, or a combination of them.

Nutritional lack, however, can play an important part in producing lesions of this type, for similar ocular findings were repeatedly induced in animals placed on inadequate diets.<sup>4</sup> Moreover, retrobulbar neuritis and allergic conjunctivitis may be related lesions, not coincidental ones. An underlying allergy may be responsible for both conditions.

In only a few of these subjects under consideration was a characteristic *chorioretinitis* discovered. It was an accidental finding, the inflammation not giving rise to any subjective symptoms. The condition was seen in the course of a consultation for some other irrelevant complaint. The chorioretinitis involved the macular region, though never precisely invading the fovea centralis. Vision in all cases was preserved. The pathologic area, approximately the diameter of the disc, usually consisted of a ring of small circular depigmented spots of a yellowish-pink color, and in this group all of the spots had shown activity of different degrees. They were seen in men of all ages. These patients included those who proved normal in every type of clinical investigation—general medical, nose and throat, dental, genito-urinary—and in blood and urine examinations. Their only treatment was dietary. In a few days they rapidly recovered on the diet served, mainly consisting of a variety of fresh foods—milk, eggs, fruits, meats and vegetables, infrequently fortified with a supplement of multiple vitamins. As the spots improved, the usual process was observed to take place, a proliferation of pigment at the periphery of each small pink circle. With complete healing, a sharp line of demarcation separated the healthy retina from the formerly inflamed zones.

Rarely, another type of chorioretinitis was noted—*chorioretinitis juxtapapillaris*. In this affection also the unhealthy membranes improved in a few days after the institution of a changed diet of vastly superior food, without medication.

## COMMENT

The findings verify observations that have been made by others, namely, that ocular signs of systemic disease may occur before other manifestations become sufficiently evident to warrant a correct diagnosis.

In the patients considered in this report, there was a basic disturbance in metabolism of nutritional origin. Except for the chorioretinitis, each of the conditions discussed—myopia, night-blindness, vernal catarrh or allergic conjunctivitis, hazy fundus oculi, pallor of the optic disc and retrobulbar neuritis—has been shown to have an etiological dietary background, the extent of which in relation to other causative factors has not been thoroughly explored. There is no doubt, however, that malnutrition figures prominently in causation.

Those subjects exhibiting vernal catarrh, optic nerve disease and chorioretinitis responded well and quickly to the new diet when nutritional lack was a prime cause. They showed improvement within a matter of days. The progress of the myopic patients could not be followed over a long enough period of time, for months of study would have been necessary in order to draw any conclusion. Ample research, however, already has been done to establish the need for proper nutrition in myopia.

Common to all of the patients is the fact that apart from the eye signs they did not reveal any clinical evidence of malnutrition in other tissues. The men all appeared healthy. That is, the systemic deficiency was apparently latent. The eye signs were the sole manifestations of the metabolic disorder.

Similar conditions prevailed during many of our investigations on animals made in the Department of Pharmacology of the College of Physicians and Surgeons, Columbia University.<sup>5</sup> In one report many ocular lesions were described in groups of animals placed on diets in which definite nutrients were omitted—vitamins A, B and D—and in a further group on a low caloric intake. It was noted that “with the exception of retarded growth, the eye lesions were the first pathologic features to be observed.”

Naturally, in a study of this type, no large enough groups from the same ship or compound could be observed. Neither could the diets be furnished on the various ships, in the fields and at different bases be checked, nor could the hospital menus be analyzed carefully from a

quantitative and qualitative point of view. It may be taken for granted that the diets served at our base hospital, situated in a fine food producing country, were far superior to those received by the men at their battle stations. Particular attention was paid to the milk intake. A quart daily was advised to give the optimum of a gram of available calcium.

Frequently, the diets were also fortified with supplements of vitamins A, B, C and D. The importance of vitamin D especially was stressed, for the lack of it may be a potent cause of eye disease. Comparatively high doses of the vitamin D were prescribed for all patients with progressing axial myopia, vernal catarrh and night-blindness.

#### CONCLUSION

In a group of patients in the armed forces suffering from faulty food intake, certain eye conditions have been demonstrated—axial myopia, vernal catarrh (also called allergic conjunctivitis), hazy fundus oculi, chorioretinitis and optic nerve disease. These findings further substantiate earlier animal and human research.

When there are no other clinical signs or symptoms of inadequate feeding in a patient, examination of the eyes may reveal the only evidence of malnutrition. Hence, the eye may serve as a guide to latent nutritional deficiency diseases.

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BULLETIN OF THE NEW YORK  
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BULLETIN OF  
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MAY 1946

THE SURGICAL TREATMENT OF  
CHRONIC DUODENAL ULCER \*

J WILLIAM HINTON

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THE value of surgery as the procedure of choice in the treatment of chronic duodenal ulcer is dependent upon the results of previous medical management. Analysis has shown that surgical failures are often due to inadequate preoperative medical care, or occur when surgery is used as a short cut to restoring the patient's earning capacity. In the latter instance it has been found that this is best accomplished by medical care.

Our observations in the Stomach Clinic of the Fourth Division of Bellevue Hospital over the past 18 years have shown that chronic duodenal ulcer can be treated most satisfactorily on a medical regimen. Of 1256 stomach ulcers reviewed in 1942,<sup>1</sup> 89 per cent were duodenal. Over a fourteen year period we had 993 unoperated cases and in only 14 per cent of these was operation advised. During 1942 and 1943, eighty-five operations were reported<sup>2</sup> of which nineteen, or 22 per cent, had been surgical failures from a previous operation. On the basis of these observations it seems apparent that through an appreciation of the

\* Read before the Section on Surgery of The New York Academy of Medicine December 7, 1945.

value of prolonged medical treatment, a high percentage of surgical failures can be avoided

### INDICATIONS FOR SURGERY

The indications for surgery frequently discussed in the literature are pyloric stenosis, recurrent hemorrhage, penetrating ulcers, lack of cooperation on the part of the patient under medical management, and intractable pain. In my opinion the last mentioned condition is the one real indication for surgical intervention.

The stenosing and obstructing ulcer has recently been reviewed by Allen<sup>3</sup> who feels that the stenosing lesion finally becomes a mechanical problem and the patient seeks help because he can no longer absorb nourishment to maintain life. The onset of such a condition is gradual and the end-stage is reached so insidiously that frequently the stomach is found to be enormously dilated. It is remarkable that such an organ, emptying infinitesimal amounts of its contents into the duodenum causes so little distress. In the two clinics with which I am associated, it has been our experience that a patient with a stenosing or obstructing ulcer can be relieved by medical management, unless he is suffering severe pain. In the past thirteen years no patient with so-called pyloric obstruction unaccompanied by severe pain has been referred for surgical intervention. Many have been advised against operation.

Wilkinson<sup>4</sup> emphasizes that an obstruction of not more than three months' duration will respond satisfactorily to medical management but if an obstruction has been present for more than three months, recurrences are almost certain and operation is usually indicated. He does not mention pain as a factor in causing the obstruction. In our experience, obstruction without pain is due to edema and pylorospasm and not to scar tissue around the pylorus.

Massive hemorrhage, occurring once or oftener as an indication for surgery is a controversial question. It is difficult to differentiate between massive and moderate hemorrhage, and a study of the literature reveals a marked elasticity in the grouping of these cases. However, if we agree that a red blood cell count of 2,000,000 or less, a hemoglobin reading of less than 40 per cent, and lowered blood pressure with a moderate degree of shock, constitute massive hemorrhage, we can discuss the severe hemorrhages with better understanding.

Surgical management of massive hemorrhage may be considered un-

der two headings surgical intervention in the stage of acute hemorrhage, which is occasionally indicated, and second, surgery as an elective procedure to prevent further hemorrhage. My views regarding the first mentioned type of management have been expressed in a previous publication.<sup>5</sup> The indications for surgery as an elective procedure are interpreted differently in different hospitals. The point emphasized by Allen<sup>3</sup> as to the dangers of massive hemorrhage in the different age groups has been fairly universally accepted. That is, in a patient over forty-five years of age, the prognosis is serious, while in a patient under forty-five, massive hemorrhage rarely proves fatal. Blackford and Allen<sup>6</sup> in a report of 151 fatal hemorrhages, record that in only thirty-five cases, or 23 per cent, was there a history of previous hemorrhage, in other words, 77 per cent of the fatalities occurred following the first hemorrhage—an interesting observation. These authors also observed that 34, or 23 per cent of the deaths, occurred at home, that is, about one in four patients died without reaching a hospital.

The management of the patient who has had a massive hemorrhage or even two and occasionally three massive hemorrhages will depend not so much upon the fact that he has had one or even three massive hemorrhages as upon the x-ray findings and his clinical history. From my experience, the patient with a massive hemorrhage who is not suffering pain of the chronic intractable ulcer seldom, if ever, requires operative intervention as an elective procedure.

If the patient is suffering severe pain associated with massive hemorrhage, then the indications are present for operative intervention. The hemorrhage is merely another indication that the ulcer has progressed to such an extent that the patient will obtain no further benefit from conservative measures and continued medical treatment may endanger his life from a sudden hemorrhage due to an erosion through the superior pancreaticoduodenal artery.

The penetrating or perforating duodenal ulcer, as diagnosed roentgenologically, does not necessarily constitute a true indication for surgical intervention. Here again, we must rely on the clinical evaluation of the symptomatology. If the patient has had an ulcer for years, with intractable pain, then the indications are obvious, but if he has had an ulcer for only a short period of time, and it proves to be a penetrating ulcer, medical management will very frequently relieve the symptoms and the niche will disappear.

Patients who will not cooperate under medical management should not be operated upon. If the surgeon accepts this type of patient for operation the results from surgical procedure will be unsatisfactory.

### OPERATIVE PROCEDURES

Before evaluating the different operative procedures for chronic duodenal ulcer, let us consider the physiologic principles involved. The etiology of ulcer is unknown but it is admitted that excessive secretion of acid is an important factor in its aggravation and possibly its production. We must realize that excessive acid is only one phase of the physiology of the stomach. Wolf and Wolff<sup>7</sup> have graphically illustrated the phases of gastric physiology in their clinical observation of a patient on whom a gastrectomy was done for a stricture of the esophagus. Their careful observation brings out three clearly correlated factors: hyperemia, hypersecretion, and hypermotility. When one of these is increased or decreased, all are affected. These authors showed that excitement or anger will cause an increase in secretion and motor activity, and redness of the gastric mucosa. Depressing states will contrariwise depress all of these functions, but they are never entirely eliminated. There is always a moderate degree of secretion, motor activity and hyperemia in the resting stomach. With excessive secretion of hydrochloric acid there is likewise an excess of pepsin and mucus, or the alkaline component of the stomach. The mucus neutralizes the acid, and when 20 cc. of 0.1 normal hydrochloric acid was given it did not increase gastric acidity, but caused an increase in mucous secretion. They found that 20 cc. of .34 normal hydrochloric acid had an even more pronounced effect on mucous secretion.

The emotional state of the individual has a marked effect on the gastric function. Mental depression is accompanied by depression of the gastric function. On the contrary, mental tension is accompanied by an increase in gastric function. These observations are important when we speak of treating duodenal ulcers by operative procedures based on physiologic principles.

The choice of gastroenterostomy as an operative procedure is based on the belief that gastric acidity is reduced by the influx of jejunal contents and the ulcer has a chance to heal. Lannin<sup>8</sup> believes that the alleged benefits from a gastrojejunostomy are due not only to the new avenue of escape for the stomach contents but also to the regurgitation

of the alkaline duodenal juices into the stomach with neutralization of the gastric secretion. Although in my experience the gastric acidity was usually lower following a gastrojejunostomy, none of the patients with duodenal ulcer studied was persistently achlorhydric, and the incidence of jejunal ulcer was 10 per cent.

Balfour<sup>9</sup> states that in his opinion it is not always advisable to remove a lesion situated on the posterior wall of the duodenum if the removal of such a lesion introduces considerable operative risk, and it should be kept in mind that an indirect procedure will bring about healing of the ulcer. He believes that it is a principle in gastric surgery that any operation which has ever been designed for treatment of peptic ulcer, whether it is a partial gastrectomy or a gastrojejunostomy, is based on physiologic principles.

Heuer and Holman<sup>10</sup> studied the gastric acidity by the histamine method in a follow-up of seventy-five patients following gastroenterostomy. They found that in fifty-six, or 75 per cent of the cases studied the end results were satisfactory after a period of from six months to ten years. In sixty-nine, or 92 per cent, free hydrochloric acid was found to be present in normal amounts, and in the majority, greater than normal. In only 6 or 8 per cent was the acidity below normal.

Walters, Gray, Priestley and Counseller<sup>11</sup> reporting on surgery of the stomach and duodenum at the Mayo Clinic for 1942 are of the opinion that in the future operative procedures for duodenal ulcer will be about equally divided between gastric resection and gastroenterostomy, with a few miscellaneous procedures done each year.

Finsterer's report in 1918<sup>12</sup> advocating gastric resection with exclusion of the pylorus marked the beginning of radical surgery for chronic duodenal ulcer. Lewisohn<sup>13</sup> at Mt. Sinai Hospital was the first in this country to advocate subtotal resection as an operation of choice in chronic duodenal ulcer, and most of us are familiar with the criticism directed at their work for at least a decade.

While the end-results of gastroenterostomy for duodenal ulcer unquestionably have been satisfactory in a certain percentage of cases, the percentage of good results is very small in cases of true penetrating duodenal ulcers where the floor of the ulcer is formed by an adjacent viscus. Rarely have satisfactory end results been observed in the Stomach Clinic of the Fourth Division at Bellevue Hospital in this type of case.<sup>14 15</sup> We concluded some 14 years ago that patients who can be helped by a gas-



troenterostomy can usually be helped by a prolonged medical regimen

Subtotal gastrectomy has been accepted as the operative procedure of choice in chronic duodenal ulcer in a number of the clinics, particularly during the past 10 years. One should not be misled by the term subtotal gastrectomy as there is considerable difference of opinion as to what this constitutes: first, the percentage of stomach removed, second, whether the entire antral mucosa has been removed, and third, whether the duodenal ulcer is removed *in toto* or left *in situ*. In the two clinics with which I am associated, we feel that those patients who do not have the duodenal lesion removed have more complaints than those in whom it is removed. There is accumulating evidence to the effect that leaving the pylorus or antral mucosa definitely increases the incidence of gastrojejunal ulcer.<sup>16, 17, 18</sup>

McKittrick, Moore and Warren,<sup>19</sup> reporting on a two-stage operation for chronic duodenal ulcer in a patient 76 years of age, found that the patient did so well following the first stage operation that his attending physician was hesitant to have the second operation performed. After three months, however, signs and symptoms of a jejunal ulcer developed and seven months later the patient returned for a second stage operation. The roentgenograms showed a large jejunal ulcer. The routine second stage operation was carried out and the region of the previous anastomosis was not entered. The pain disappeared and 11 days postoperatively the roentgenologic examination showed a marked decrease in the size of the ulcer. Eight months later the patient was perfectly well. Friedell, Shaar and Walters<sup>16</sup> of the Mayo Clinic have had similar experiences. Jordan<sup>18</sup> of the Lahey Clinic reports an even more dramatic case of recurring jejunal ulcers with repeated massive hemorrhages. In this patient the pylorus was removed 12 years after the original operation with disappearance of the gastrojejunal ulcer and cessation of the massive hemorrhages.

The antral mucosa is the source of gastrin or internal secretion as described by Edkins in 1906,<sup>20</sup> and, unless the antral mucosa is completely removed, we have in effect an organ of internal secretion constantly supplying gastrin to the blood which stimulates the acid cells of the fundus of the stomach. The surgeon would hardly be justified, therefore, in leaving the antral mucosa if he hopes to obtain the most satisfactory end-results in chronic duodenal ulcer.

The advisability of leaving the ulcer *in situ* or of removing it *in toto*

is still a controversial question. In 1945 Rienhoff,<sup>21</sup> reporting on 260 chronic duodenal ulcers, advocated leaving the ulcer and doing a minimum resection. In this group of patients only 107, or 40 per cent, had no free acid after the operation. Twenty-three, or 9 per cent, developed jejunal or marginal ulcers. Colp, Klingenstein, Mage and Druckerman<sup>22</sup> state they do not feel that excision of the ulcer is an essential part of the procedure, provided the pylorus is removed. Mage<sup>23</sup> in a follow-up study of patients on whom subtotal gastrectomy had previously been performed concludes that recurrent gastrojejunal ulcer was no more frequent in those patients in whom the duodenal ulcer was left *in situ* than in those in whom it was excised. Colp et al<sup>22</sup> in their series of 223 chronic duodenal ulcers, performed a subtotal gastrectomy in 77.6 per cent, a posterior gastroenterostomy in 21.5 per cent and a pyloroplasty in 0.9 per cent.

Two questions that constantly arise in a discussion of operative procedures are, first, the end-results, and second, the mortality rate. In this presentation I propose to review the operations I have performed during the past ten years for chronic duodenal ulcer, and determine the end-results and the mortality rate, with emphasis on the incidence of gastrojejunal ulcer.

During a ten year period from 1935 to 1944 inclusive I have had occasion to operate upon 162 patients, either service or private, for chronic duodenal ulcer. The cases I am reporting are primary operations, all secondary operations are excluded. Likewise, the patients operated upon as a life-saving measure during an active massive hemorrhage are excluded. Of these 162 patients, 92 per cent were males and 8 per cent, females. The average age was thirty-eight and symptoms had been present for 7.5 years. The one indication for operation was chronic intractable pain. In 17 per cent of the patients there had been one or more massive hemorrhages accompanied by severe pain. In 10 per cent of the cases there was an associated pyloric obstruction with gastric retention. There was evidence of perforation of the ulcer into the head of the pancreas or the duodenohepatic ligament in 135 or 83 per cent. Seventeen or 10 per cent were multiple duodenal ulcers.

For the past twelve years I have followed the same technique in all operations, namely, between 65 and 70 per cent of the stomach is removed and the duodenal ulcer is always removed *in toto*. In my opinion the ulcer can always be removed, but it requires care to obtain

a line of cleavage between the duodenum and the adherent pancreas. The question is raised by some roentgenologists as to whether the ulcer has been removed if the pathologist does not report it in the specimen. The answer is that in the patient with a long history of ulcer with severe pain, no ulcer as such is present but there is a penetration through the entire duodenal wall from 1-3 cm and the pancreas forms the floor of the ulcer. When the duodenum has been freed from the pancreas there is no ulcer to present unless a portion of the pancreas is excised, and this is, of course, never indicated. The freeing of the duodenum from the pancreas and the closure of the duodenal stump are the most important steps in a subtotal resection. If the ulcer is left *in situ* the end results are not as satisfactory as when it is removed *in toto*. The mortality in most cases is due to leakage from an insecurely closed duodenal stump. The stump is always sutured with five rows of cotton sutures, the fifth row burying the stump in the head of the pancreas.

The continuity between the jejunum and the stomach is accomplished by an antecolic short-loop anastomosis, utilizing the entire end of the stomach to approximate to the jejunum and starting the jejunal anastomosis at the greater curvature of the stomach  $3\frac{1}{2}$  to 5 inches below the ligament of Treitz. Enteroenterostomies are never performed in an antecolic anastomosis even if the procedure is a total gastrectomy for carcinoma. Fine catgut is used for the jejunum-to-stomach anastomosis. Fine cotton was used for two years but was discontinued over two years ago when a gastrojejunal ulcer was met in a primary resection.

In the 162 primary resections there have been six deaths, or a mortality of 3.7 per cent. Of the 156 surviving patients we have a follow-up on 135, or 86 per cent. These cases are now from one to 10 years post-operative, averaging 3.8 years. Among these surviving patients there is one gastrojejunal ulcer, a case in which cotton was used in the anastomosis. This patient has been reoperated upon and is now well three years after the second operation. Two other patients are suspected of having gastrojejunal ulcers. One is a woman who has had recurring hemorrhages, and the other is a man who is having severe pain. There are 10 other patients with minor complaints, but in none of these is there any suspicion of a gastrojejunal ulcer and the x-rays are negative for an ulcer. However, in these cases the end results can not be considered satisfactory. We have, then, a total of 122 cases, or 90 per cent, in which the end results are excellent. It must be remembered that these

patients, although symptomless, may not regain their pre-operative weight for months or years. This constitutes a definite nutrition problem, perhaps associated with a disturbance in pepsin, lipase, and rennin secretion.

In the group of patients followed, gastric analysis has been done on fifty-two patients. The histamine technique of Bloomfield and Pollard<sup>24</sup> was used. The stomach contents were aspirated after the patient had fasted for twelve hours and then 0.1 mg. of histamine for each 10 Kg. of body weight was given subcutaneously. Continuous aspiration was employed for forty-five minutes. On the volume withdrawn at 15, 30 and 45 minutes, free hydrochloric acid was determined. It was found that thirty patients or 57 per cent had no free hydrochloric acid either on a fasting stomach or after histamine stimulation. Twenty patients or 38 per cent showed no free hydrochloric acid on a fasting stomach, but after histamine stimulation they had from 2 to 28 units of hydrochloric acid, which is low when compared with 60-120 units in a normal stomach stimulated with histamine. Two patients or 4 per cent had 4 units of acid on a fasting stomach and in one this amount rose to 59 units after histamine and in the other, to 28 units. These studies were done on patients from nine months to ten years postoperative, averaging 2.4 years.

The end-results in this series of cases seem to justify the removal of the ulcer *in toto*. The mortality rate compares favorably with most reports and the end-results seem satisfactory for such a serious disease. As the gastric physiology is rather complex, as illustrated by Wolf and Wolff,<sup>7</sup> it would seem wise for the surgeon to attack the problem of chronic duodenal ulcer as most other abdominal problems are attacked, namely, on a pathologic basis and not on the physiologic basis. We have only to review the literature of the past two or three decades to find innumerable advocates of cholecystostomy as against cholecystectomy in chronic gall bladder disease. Some of the same arguments were used then as now in regard to the adherent duodenal ulcer. Most inflammatory processes are cured by surgery, not by altered physiology.

#### CONCLUSIONS

1. This paper may be criticised because 14 per cent of the patients do not have adequate follow-up.
2. The end-results in the cases followed seem to justify the insistence on removal of the adherent ulcer *in toto*.
3. It would seem appropriate to emphasize pathologic principle.

rather than physiologic principles in the surgical treatment of chronic duodenal ulcer

4 Chronic inflammatory processes, when surgically treated require removal and the adherent duodenal ulcer is not an exception

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# THE STIMULUS OF WAR TO CARDIOLOGY\*

## *A Review*

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I n modern warfare, infectious diseases and injuries requiring surgical care are the chief concerns of the medical departments of the Armed Forces. Cardiovascular disorders among those on active duty have occupied a position of lesser importance, largely because Selective Service and pre-induction examinations have eliminated those recruits manifestly unfit because of such defects. Yet much information has been gained concerning the incidence and types of heart diseases among the population as a whole, and studies in special fields have yielded knowledge not restricted to the conditions of war. In this brief summary are reviewed only a few of the numerous investigations which have been made. Indeed, the results of many of them have not yet been published. The remarks which follow will be confined to a consideration of some of the clinical problems relating to cardiac disease in the Army, which present features of equal interest in civilian practice.

## HISTORICAL NOTE

It is doubtful whether it would be profitable to follow the heart of the soldier through all the campaigns of history, it is certainly not practicable because the necessary data are lacking. But some of the observations recorded during the past hundred years serve to reflect the changing points of view during this period. R. H. Hunter,<sup>1</sup> stationed in India, writes in 1836: "Ever since I joined the 2d or Queen's Royal Regiment in Colaba in 1831, I have been struck with the frequency of cardiac and aortic disease. Whether, or not, rheumatism be the first link in the morbid chain, a more efficient cause for hastening its progress

\* Read at the Graduate Fortnight of The New York Academy of Medicine, October 19, 1945.

I am convinced, is the active duty a soldier undergoes whilst buttoned up in his accoutrements. These, by compressing the neck and chest, obstruct the circulation to such a degree, as to excite the heart to inordinate action, and consequent hypertrophy in the strong and muscular, or to dilatation in the weak and sickly.

"It seems extraordinary that, now the effects of tight lacing on females are so well known, a soldier, intended for the most active and long continued exertion, should be placed in a similar predicament, when that very exertion is required. Is it possible he could be placed under more unfavorable circumstances?"

The role of tight clothing and heavy equipment as a cause of heart disease continued to occupy the attention of those in authority. In 1870, some thirty-four years later, Myers,<sup>2</sup> an assistant surgeon of the Coldstream Guards, won the Alexander Memorial Fund Prize for his essay, "On the Etiology and Prevalence of Diseases of the Heart Among Soldiers." The Executive Committee of the Fund, composed of distinguished physicians and high-ranking officers of the British Army, chose both the topic and the winner. The subject evidently was considered an important one.

Among Myers' conclusions were these: disease of the heart was more prevalent in the army than in the civil population, its three main causes were rheumatism, Bright's disease, and violent manual labor, syphilis, by attacking both classes to nearly the same extent, produced a relatively equal deteriorating effect, disease of the mitral was more common than disease of the aortic valve in the civil population, and aortic more than mitral in the army. In view of this higher incidence of aortic disease among the troops, the modern reader will wonder whether syphilis, after all, may not have exerted its "deteriorating effect" more frequently in the military man.

With regard to etiology, this author remarks: "there is one special cause of heart disease in our army now clearly laid down by those who have most studied the subject—viz, the prejudicial constriction of the uniform and accoutrements—this producing such obstruction to the circulation that, either directly or indirectly, as by aneurism and disease of the aortic coats, etc., the heart is abnormally strained, and frequently passes into a state of functional derangement, and ultimately of organic disease." Remedial measures were suggested and the opinion expressed that when these had been adopted heart disease would gradually

diminish in the army

In our own Civil War<sup>3</sup> organic disease of the heart was rare, only 3,778 cases having been taken to sick report on this account among the white troops during more than five years. But if discharges are taken into account, 10,636 men were lost to the service because of heart diseases. The difference between the two figures, says the official report may be regarded as expressing the results of acute rheumatism, of which 145,551 cases were registered. This is a surprisingly large number.

The occurrence of idiopathic pericarditis was specifically mentioned and there were numerous instances of sudden death, attributed to "a relaxed or degenerated heart or to the development of fibrinous concretions within its cavities." One instance of cardiac rupture, referred to as "phenomenal," occurred in a wounded man while confined to bed. Autopsy showed an adherent pericardium, there was no mention of the state of the coronary arteries or of the heart muscle.

The most important and enduring medical contribution to come out of the War of the Rebellion was the paper of Da Costa, "On the Irritable Heart. A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences," published in 1871.<sup>4</sup> Very little has been added to his description of the essential features of this condition, to which the terms effort syndrome and neurocirculatory asthenia later were applied. To this day, the basic mechanisms responsible for its manifestations are not clearly understood and furnish a subject for controversy.

#### WORLD WAR I

Once again functional disorder of the heart, now labeled "effort syndrome," was the condition subjected to most intensive study. It was a cause of much invalidism and a frequent reason for discharge in both the British and American armies. Sir Thomas Lewis and his group at Colchester<sup>5</sup> made the most detailed observations. Lewis was aware that he was describing a series of symptoms which might occur under varying circumstances—as a result of exposure and strain, during delayed convalescence and in association with active infection, particularly tuberculosis. One of his largest groups was that of constitutional weakness, nervous or physical, or both. His critical analysis served to define and stress the various clinical features. He was of the opinion that many could be cured by a system of graduated exercises, and that, in a large number, the natural course was towards recovery. Grant's follow-up



study of 665 of Lewis's cases<sup>6</sup> showed that, in them, the frequency of pulmonary tuberculosis was 80 per cent greater than in the general population of London over the same five-year period. This high incidence was due, undoubtedly, to errors in diagnosis because routine x-rays of the chest were not made. Incipient cardiac disease was shown to be the underlying cause in only a negligible proportion of the patients.

The after histories of a thousand men discharged from the British Army because of valvular heart disease were also studied by Grant.<sup>7</sup> The patients were followed for ten years. Most of them had rheumatic valvular defects, a few had syphilitic aortic disease. Those with a good prognosis showed little or no cardiac enlargement and a good exercise tolerance. Those with a poor prognosis showed moderate or great enlargement and evidences of congestive failure. The onset of auricular fibrillation influenced the general prognosis unfavorably. Grant's final conclusion was to the effect that the outlook of valve defect was not as bad as generally thought, even for syphilitic aortic regurgitation.

Some figures of interest, in relation to those of World War II, are given in the official report of the Cardiovascular Section of the Office of the Surgeon General of the United States Army.<sup>8</sup> In one million recruits, 1.5 per cent were rejected for cardiovascular reasons, 0.88 per cent with cardiac disorders were accepted for limited service only. The causes of disqualification of 11,562 recruits so rejected were: chronic valvular disease, 49 per cent; other organic diseases, 19 per cent; functional disorders, 23 per cent. The belief was expressed that the number rejected for organic heart disease—68 per cent—was too large, due to the tendency on the part of the examiners to classify functional conditions, such as irritable hearts, as instances of organic disease.

In the German<sup>9</sup> and British<sup>10</sup> official medical reports of the first World War there were no features worthy of special mention with respect to the cardiovascular system. Most of the chapter in the British report was devoted to a consideration of the effort syndrome.

## WORLD WAR II

*Neurocirculatory Asthenia* Because of the frequency, in the previous war, of the effort syndrome, or as it was now called, neurocirculatory asthenia, the importance of this condition was stressed as soon as the draft became effective. This was done in order to keep out of the

Armed Forces recruits suffering from the disorder and with the idea of learning more of its etiology. At first, cases of slight degree were accepted for service, later it became apparent that it was wise to reject even those with the mildest symptoms, for they made poor soldiers. The diagnosis, however, was not always easy. Fortunately many of these cases were excluded as a result of the neuropsychiatric examination.

In England, Wood<sup>11</sup> began work in 1940 and in May 1941 read three Goulstonian lectures on "Da Costa's Syndrome (or Effort Syndrome)." His conclusions were based on a careful clinical study of two hundred cases. It was his opinion that the central stimulus was emotional and was commonly the result of fear, that this disorder should be classed as psychiatric, and that the somatic manifestations were of secondary importance.

In this country, White, Cobb and their associates<sup>12, 13</sup> made extensive observations on cases of neurocirculatory asthenia at the Massachusetts General Hospital, in collaboration with the Harvard Fatigue Laboratory. For the purpose of investigation, they regarded as of practical importance the separation of the acute from the chronic type and confined their studies to instances of the latter variety. Only preliminary reports have been published to date, but a number of facts were established. Men with this disorder were not able to do hard work as well as healthy soldiers. Their pulse rate recovery after exercise was slower and the rise in pulse was higher. Lactic acid determinations, taken after a walk of ten minutes on a treadmill, showed a level almost twice as high in patients as in normals. The ventilation index, which is an objective measurement correlated with the subjective feeling of dyspnea, was higher in patients than in the controls. The group with neurocirculatory asthenia showed looped capillary forms in the nail folds whereas in normal persons the hair-pin type predominated. Psychological tests yielded lower scores in those with neurocirculatory asthenia. Attempts to train a selected group under the supervision of an athletic director were unsuccessful. It was concluded, tentatively, that the chronic form of neurocirculatory asthenia is not a simple disturbance of the circulation but is associated with measurable psychological symptoms, abnormal behavior and difficulty in adjusting to life situations. There was evidence, also, of a familial incidence.

Still another approach was made by Starr,<sup>14</sup> using the ballistocardiogram as an indicator. This is a record of the forces generated by

the recoil of the heart and the impacts of the blood. From it can be calculated the cardiac output. The result is not highly accurate, but there appears to be a fairly definite range of normal. It was found that most of the subjects with neurocirculatory asthenia had abnormally large impacts. Starr was not inclined to agree with the notion that the condition is a neurosis, although admitting the possible accessory role of psychic disturbances. He drew the analogy between neurocirculatory asthenia and the common clumsiness of a muscular movement which might date from early life and was perhaps hereditary. Neurocirculatory asthenia, he suggested, might be thought of as a clumsiness of the circulation, with inability to adapt it to the needs of the moment.

*Coronary Heart Disease* Fatal coronary arteriosclerosis in soldiers, 20 to 36 years of age, was the subject of a study by French and Dock.<sup>15</sup> Eighty cases examined at autopsy furnished the basis for their conclusions. The disease occurred in men of various racial stocks, without predilection for any particular one. The most common predisposing factor appeared to be overweight, which was present in 91 per cent of the patients. Vigorous effort and the activity of early morning chores brought on the attacks in over 50 per cent. Cardiac hypertrophy of significant degree did not occur in this series. Myocardial scars, indicating previous insults, were observed in 59 per cent of the cases and recent myocardial infarction was found in 19 per cent.

The direct relationship of effort to attacks of acute myocardial infarction in soldiers was further stressed by Blumgart,<sup>16</sup> who reported eleven cases. The matter is of practical importance as well as of theoretical interest. It appears to be true that the majority of attacks of coronary occlusion occur at rest, but this does not preclude the possibility that, in certain instances, exertion may be the initiating factor. There is good evidence, in civilian experience, that this is so.

*Quinidine* Before the war, most of the quinidine used in this country came from Java. The supply was abruptly cut off when the Japanese took over the island and the available stock has steadily dwindled. Cinchona bark, obtained from South America, yields comparatively little quinidine. Since this drug is useful in a number of cardiac disorders and may be lifesaving in the treatment of ventricular tachycardia, it became necessary to seek a substitute. Under the auspices of the Subcommittee on Cardiovascular Diseases of the National Research Council, comparative tests are now being made, in patients, of the therapeutic

efficacy of commercial quinidine, synthetic quinidine and dihydroquinidine. Preliminary observations indicate that all three, in proper doses, produce similar clinical effects. The final results are not yet available but should prove of practical value in the future.

*Selective Service Examinations* The numerical importance of diseases of the heart and circulation, in men of draft age, became clearly evident in the figures published in 1942 by the Selective Service System.<sup>17</sup> Following the examination of the first million registrants, 18 to 37 years of age, it was estimated that 10.6 per cent were unqualified for general military service for cardiovascular reasons. Only defects of the teeth and eyes were responsible for a larger number of rejections. In 1944, after examination of 4,049,000 registrants of similar age groups, 58 per cent were disqualified for physical defects.<sup>18</sup> Of these, 6.5 per cent were rejected because of cardiovascular diseases.

*Reexamination of Cardiac Rejectees* Because these rates seemed excessive for the age period covered, it was suggested by the Subcommittee on Cardiovascular Diseases of the National Research Council that one thousand men rejected for cardiovascular reasons be reexamined in each of five cities by boards of cardiologists. The plan was promptly approved by Major General Lewis B. Hershey, Director of the Selective Service System. Boston, Chicago, New York, Philadelphia and San Francisco were designated as the places in which the pilot tests should be made, because they could be carried out in large general hospitals with adequate facilities. The objects of the study were first, to obtain a more detailed analysis of problems of cardiovascular diagnosis and to define more clearly the range of the normal heart, second, to determine the possible amount of salvage of men for military service, and third, to compare the opinions of cardiovascular experts with those of examiners in the local boards and induction stations. In addition to the usual history and physical examination, an electrocardiogram and 2-meter film of the heart were taken in every case considered suitable for reclassification as 1A. The final analysis was based on the reexamination of 4,994 men.<sup>19</sup>

The following is a brief summary of the results.

1. Of the total number, 17 per cent were resubmitted as suitable for Class 1A, 83 per cent were confirmed as belonging to Class 4F.

2. The chief cause for final rejection was rheumatic heart disease which was found in 60 per cent of the final 4F group. Mitral disease was

more common than that of the aortic valve. Auricular fibrillation complicating mitral stenosis, was observed in only 24 cases.

3 The second most common cause for rejection was hypertension which was found in 26 per cent. The majority showed elevation of both systolic and diastolic levels. The incidence was higher in the fourth than in the third decade.

4 Responsible for the rejection of between 4 and 5 per cent were, in order, neurocirculatory asthenia, sinus tachycardia and congenital heart disease. In the congenital group, the most frequent diagnosis was ventricular septal defect, which was present in more than a third of the cases. Next came patent ductus arteriosus, pulmonary stenosis (two with the tetralogy of Fallot), coarctation of the aorta, auricular septal defect and subaortic stenosis.

5 Other less common causes for rejection included cardiac enlargement alone, as determined by x-ray examination, and arrhythmia including paroxysmal tachycardia, uncomplicated auricular fibrillation, auricular flutter and auriculoventricular block. Electrocardiographic abnormalities alone were found in 32 cases, including 10 with bundle branch block. Cardiovascular syphilis was rare, having been found in 17 cases. The diagnosis of coronary heart disease was made in only 6 cases.

6 A history of rheumatic fever was found in a little over one-fourth of all the cases of rheumatic heart disease. This figure was based on data obtained in four of the cities. However, a positive history was noted in nearly half of those in Boston and New York. A history of chorea was rare, having been obtained in only 2 per cent of the rheumatic cardiac cases.

7 Nine of the seventeen cases of aortic syphilis were observed in negroes. Hypertension was more common in the black race. Rheumatic heart disease was evenly represented among whites and blacks but neurocirculatory asthenia was infrequent in the negroes.

As a result of these examinations, it was concluded that their extension for the sake of salvage alone was of doubtful value because of the time required, the few expert examiners available and the relatively small percentage of men reclassified as 1A. But some of the lessons learned proved helpful in later examinations, and the uncertainty concerning the significance of transient hypertension stimulated the series of "Studies of Blood Pressure in Army Officers," to which reference will be made shortly.

A follow-up study of the men reclassified as 1A has been initiated and will be completed with the help of the Veterans' Administration. In these cases there was a difference of opinion between the special boards appointed for the reexamination study and the local boards or induction stations, which had rejected them. The after histories of this group of border-line cases finally accepted for service, should prove instructive.

*Effectiveness of Selective Service Examinations* Three reports have been chosen to illustrate this point. The first was from the Medical Processing Unit and the Station Hospital at the San Antonio Aviation Cadet Center.<sup>20</sup> During a number of months, approximately 45,000 men, between 18 and 27 years of age, were examined. Only 100 were found to have rheumatic valvular disease and of this group, 11 knew of the presence of a heart murmur when in civilian life. This is an incidence of approximately 0.2 per cent. The most common lesion was aortic regurgitation, mitral stenosis was second in the order of frequency.

Another report, from the Navy,<sup>21</sup> was based on the experience of a hospital ship in which there were 9,085 admissions and that of a base hospital in which there were 13,000 admissions. On the ship, 55 patients were found to be suffering from valvular heart disease, degenerative heart disease or functional cardiac disorders, this is an incidence of 0.6 per cent. In the base hospital, 88 patients were found to be suffering from cardiac disorders—an incidence of 0.67 per cent. Sprague and McGinn, who made this study, were impressed by the relative infrequency of neurocirculatory asthenia.

The third report was a summary of the Army's experience with discharges of enlisted men for physical reasons.<sup>22</sup> During the 12 months between July, 1943 and June, 1944, 6.5 per cent of discharges were for cardiovascular diseases. This group was fifth on the list, in which neuropsychiatric disorders led by a wide margin. Cardiovascular diseases appeared to be more common among men who had not been overseas. This was not surprising, for rheumatic fever in the camps at home undoubtedly was responsible for many of these cases, and most of those with cardiac lesions were eliminated during the training period, so that they were not sent out of the country.

*Studies of Blood Pressure in Army Officers* The range of the normal blood pressure, both systolic and diastolic, is still not clearly defined. Transient hypertension, due to emotion or some other cause not apparent, has been recognized but discounted by the Army. In Mobilization

Regulations 1-9, issued by the War Department in 1942, it is stated that "if the blood pressure appears to be abnormally high, it will be measured after the subject has rested in the recumbent position." A cause for rejection is "a persistent blood pressure at rest above 150 mm systolic or above 90 diastolic unless, in the opinion of the medical examiner, the increased blood pressure is due to psychic reaction and not secondary to renal or other systemic disease." "Elevation of blood pressure from excitement proved to be temporary," is not a cause for disqualification. Because of the large number of recruits who showed such temporary elevations, it seemed important to determine their significance as soon as possible.

The records of some 23,000 Army officers on file in the Office of the Surgeon General furnished a ready material. These contained the results of annual physical examinations made between January, 1924 and December, 1941, in more than 1,800, additional information was obtained as far back as 1901. Annual examinations were discontinued in 1941, owing to the pressure of work essential to the war.

A contract was recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University, and the work of analysis was undertaken by Drs. Levy, Stroud and White of the Subcommittee on Cardiovascular Diseases of the National Research Council, in collaboration with Brigadier General Charles C. Hillman, U. S. Army. Dr. John W. Fertig, Professor of Biostatistics, Columbia University College of Physicians and Surgeons, aided in the analysis and preparation of the material for final presentation. The method of person-years was used in calculating the results.

A total of 22,741 cases proved to be suitable for study.<sup>23</sup> The average length of the observation period was 12 years. Seventy-two per cent were under observation from 5 to 19 years and 38 per cent were observed from 15 to 19 years. In 1,437 cases, or 6 per cent of the total, the observation period was 20 years or over. The specific indexes chosen to demonstrate the influence of transient hypertension on the subsequent state of health and cause of death were (1) the later development of sustained hypertension, (2) the disability retirement rates with cardiovascular-renal diseases, and (3) the death rates with cardiovascular-renal diseases.<sup>24</sup>

The frequency with which transient hypertension was first noted

increased with age. The curve of increase was smooth, beginning with an incidence of 6 per cent in the age group 25 to 29 and reaching a plateau of 19 per cent at 50 to 54. At all ages, sustained hypertension developed more frequently in those with previous transient hypertension than in those who never showed an elevation of blood pressure. In both groups, the rate increased with advancing years.

The rate for disability retirement with cardiovascular-renal diseases, which is one index of the usefulness of an officer to the Army, was consistently higher in those with previous transient hypertension than in those with normal pressure levels, at all ages from 35 to 60. The death rate was also higher in those with transient hypertension and the figures rose in the older age groups.

In the study just mentioned, the group with transient hypertension was dealt with as a whole and no attempt was made to ascertain possible differences in the prognostic importance of various systolic and diastolic levels. To obtain data on this point seemed the next logical step in the inquiry.<sup>25</sup> It was found that all levels of transient hypertension, both systolic and diastolic, were significant in terms of the later development of sustained hypertension and retirement with cardiovascular-renal diseases. Of particular interest was the observation that slight degrees of elevation were important, even when the systolic level alone was involved. Of the greatest significance, however, was a transient rise in diastolic pressure above 100 mm, especially as an early sign of subsequent sustained hypertension.

No significant differences were apparent between the various degrees of transient hypertension in relation to the death rates with cardiovascular-renal diseases. Thus, a temporary rise in blood pressure does not appear to foretell the rate of progress of vascular disease or the extent or severity of the lesions which eventually cause death.

These data lend support to the view that transient elevations of blood pressure, above the upper range of normal, often represent an early stage of hypertensive vascular disease.

Many of the registrants with transient hypertension also showed transient tachycardia. By transient tachycardia is meant a pulse rate of 100 or over, which is not persistent and not due to paroxysmal tachycardia. Army Regulations provide that a candidate is not acceptable who shows "a persistent heart rate of 100 or over when this is proved to be persistent in the recumbent posture and on observation and reexamina-



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THE RATIONALE OF PORTACAVAL  
ANASTOMOSIS\*

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SOME of the cirrhotoses, certain of the hepatosplenopathies and many of the congestive splenomegalies have some common manifestations, usually evidences of long-standing chronic lesions

Two symptoms that have always been dreaded, by patient and physician alike, are ascites and gastrointestinal hemorrhage. These are omens of serious pathology, usually associated with severe liver damage or portal hypertension or both. The ascites usually recurs after paracentesis, and once hemorrhage has occurred as a result of ruptured esophageal varices recurrent bleeding is common and sooner or later fatal. The dread of these symptoms by physicians is due to the fact that in the past no adequate therapy has been found and any new method that offers hope of dealing with these two symptoms deserves careful trial and evaluation.

The ascites is usually associated with liver damage and abnormal serum protein findings, especially a reversed albumin-globulin ratio. The severe hematemesis is usually from ruptured esophageal varices, the result of a portal hypertension, caused by either an intra- or extra-hepatic portal block. In some of the cirrhosis cases less severe bleeding occurs into the gastrointestinal tract, over a period of days or weeks, resulting in a persistent anemia, the loss of blood is due to a persistent oozing from the mucosa of the intestinal tract associated with a prolonged prothrombin time, the result of a severely damaged liver.

In the patients with ruptured esophageal varices due to portal hypertension the portal block may be intrahepatic, in a cirrhotic liver, or extrahepatic with normal liver, and a congestive splenomegaly and distended portal radicals.

\* From the Department of Surgery, Columbia Presbyterian Medical Center, New York.  
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It is obvious that any therapy to combat either one of these major symptoms or both must be preceded by a most careful study of the patient, to determine as far as possible the presence of a normal or a damaged liver and the presence of an intra- or an extrahepatic portal block. In such a study certain liver function tests as well as the physical findings, such as abdominal ascites, dilated superficial abdominal veins and cirrhotic facies, the size of the spleen, x-ray studies of the esophagus, are all important in differentiating intra- and extrahepatic lesions.

It is obvious that whether the portal block is intra- or extrahepatic the blood entering the liver by the portal vein is diminished in proportion to the narrowing of the diameter of the portal radicals. Nature provides a variable amount of shunting of portal blood to the systemic venous system by new dilated veins that develop from potential anastomotic veins in the abdominal wall, the retroperitoneal areas around the kidney and diaphragm, and between the veins around the esophagus and the azygos system and the hemorrhoidal plexus and the branches of the internal iliac veins. Any shunted blood has to pass through the systemic veins and lungs and reaches the liver with arterial blood through the hepatic artery.

Undoubtedly a relatively normal liver with extrahepatic portal block can utilize such by-passed blood more readily than a severely damaged cirrhotic liver, especially if some of the portal blood is still reaching the liver through narrowed intrahepatic portal channels. In the cirrhotic group the portal hypertension is usually not as high as in the cases with extrahepatic block, but because of abnormal albumin-globulin ratios ascites is more often present. In the patients with extrahepatic block with hypertension causing esophageal hemorrhage the shunting of the blood from the portal vein to the systemic system is more necessary and better tolerated by the liver for there is less blood reaching the liver by way of the portal.

✓ For many years attempts at shunting procedures have been tried with a sound rationale, but have proved generally unsuccessful because of the small vessels used in the shunting operations, the suture techniques used and the failure to use the supportive measures now available in the preoperative, the operative and the postoperative periods. These attempts have utilized branches of the mesenteric veins and smaller venous channels such as the ovarian and spermatic veins. The Eck fistula procedure was tried in a number of patients in France and Germany in

1910-1912 but with only one six months survivor. The cause of the prohibitive operative mortality was most frequently a renal shutdown, largely the result of shutting of the vena cava for too long a period during the suture anastomosis of the portal vein to the vena cava.

For many years one of our most discouraging follow-up problems in our Spleen Clinic at the Medical Center has been that of dealing with recurring hemorrhage in patients who had had a splenectomy for congestive splenomegaly or Banti's syndrome. Efforts at suture anastomosis of the smaller portal and systemic veins had been unsuccessful. We had encountered the problem of ascites and hemorrhage repeatedly without any promise of a successful therapy. But following Dr. Blakemore's brilliant results in bridging defects in large arteries and veins by means of direct anastomosis or by vein grafts, using vitallium cuffs to evert ends of the vessels to provide endothelium to endothelium anastomoses, this method offered definite promise in uniting the larger trunks of the portal system to those of the vena cava and ultimately of carrying out an Eck fistula in selected cases.

These portacaval shunt operations are very difficult and are still in the experimental stage and Dr. Blakemore, Dr. Humphreys and I have not done enough of them or followed the cases operated upon long enough to make any positive or dogmatic statements. But certain of our patients have shown some unexpectedly good results and we have been encouraged to attempt more of these procedures in a group that are otherwise doomed. What is most important from now on is to determine more definitely the best procedure for the patient with intra- or extrahepatic block, and to establish better criteria for differentiating the various lesions giving rise to the arresting symptoms of ascites and gastrointestinal bleeding.

Dr. Hanger will discuss the latter problem and Dr. Blakemore will present the technical operative problems and the results thus far observed. This presentation is from the Combined Spleen Clinic in which a team of internists, pathologist and surgeons have been cooperating.

## PORTACAVAL ANASTOMOSIS A REPORT ON FOURTEEN CASES\*

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THE operation of portacaval anastomosis for the relief of portal hypertension has been performed in fourteen patients. In four of the cases the site of the portal bed obstruction was extrahepatic. In the ten remaining cases the site of the portal obstruction was intrahepatic due to portal cirrhosis of the liver. There were two operative deaths, both cirrhosis cases, one occurred a few hours after operation and the other four days following operation.

Splenectomy and left nephrectomy with anastomosis of the splenic vein to the stump of the left renal vein has been performed six times, one, employing the Carrel suture technique and in the remaining five cases the non-suture technique was employed, using vitalium tubes. In a case of a nine year old boy with cavernomatous transformation of the portal vein who had previously had a splenectomy, the stump of the splenic vein was isolated and anastomosed to the vena cava, end to side employing the suture technique. In the remaining seven of the fourteen cases, the portal vein was anastomosed to the vena cava end to side (Eck fistula) using the non-suture technique with vitalium tubes.

Whereas the follow up results in the four cases of portal hypertension due to extrahepatic portal block have not been ideal, the operation appears to have been distinctly beneficial in three of the four cases. It is true that three of the four cases have had episodes of bleeding since operation, but in general the bleeding episodes have not been as severe or as frequent as before operation. No case has had hematemesis as was the rule before operation. We now have a follow up of one and one-half years on a sixteen year old girl who, for years before operation had had massive hematemesis followed by tarry stools of two weeks duration. During the year prior to operation the attacks occurred at

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approximately six month intervals. Whereas, since the performance of a spleno-renal shunt one and one-half years ago there have been only two bleeding episodes, one of which was so slight as to be considered negligible and in neither was there hematemesis. A follow up letter from the patient dated January 9, 1946, states there has been no bleeding since March 1945 (nearly a year). She states further that her general health is much improved, has more energy and does not tire easily.

An esophagram made one year following operation on this girl, when compared with an x-ray taken before operation, revealed a marked reduction in the size of the esophageal varices. It is reasonable that this evidence of reduced pressure in the portal system so lessens the strain upon the esophageal vessels as to permit the strengthening processes within the vein walls an opportunity to become effective against erosion or sudden rupture.

This patient had an obstructive lesion (cavernomatous transformation) of the portal vein. One cannot in such case of portal vein obstruction expect the splenic vein, when used to effect a portacaval shunt, to reduce the portal pressure to anywhere near a normal figure. It must be remembered that the splenic vein handles normally only approximately 40 per cent of the total volume blood flow of the portal system. As a matter of fact, opening the spleno-renal shunt at operation in this case reduced the pressure in the superior mesenteric vein from 390 mm of water to 290 mm of water—a reduction of 100 mm in portal bed pressure. Although this is far from the normal figure of 100 mm of water, it is a great stride in the right direction for this girl and, it may mean just sufficient reduction in portal pressure to change her future from the certainty of a lethal bleeding episode.

The amelioration of the viciousness and frequency of bleeding episodes in this girl and others commends the procedure of portacaval shunt to further trial upon a group of otherwise hopeless cases. Cases of extrahepatic portal block, e.g., cavernomatous transformation of the portal vein, are unsuitable for the establishment of Eck fistulae. An attempt to do so, using a vein graft to bridge the distance from the foreshortened portal vein to the vena cava accounted for our one total failure in the group of four cases of portal hypertension due to extrahepatic portal bed block.

Because of the greater size of the portal vein, its anastomosis to the vena cava (Eck fistula) will shunt a far greater volume of blood than

a spleno-renal anastomosis, which, in effect makes the Eck fistula a more efficient shunt for the lowering of portal pressure. For the above reason and the fact that Eck fistula operations seem to be better tolerated than spleno-renal vein anastomoses we now prefer its use in cases of cirrhosis of the liver.

Of the eight cases of cirrhosis of the liver followed postoperatively four had splenectomy, left nephrectomy with anastomosis of the splenic vein to the renal vein stump and four had anastomosis of the portal vein to the vena cava (Eck fistula).

The indications for portacaval shunt are clear cut in cases of portal hypertension when due to extrahepatic portal bed block. Whereas, in cases of cirrhosis of the liver the problem is more complex. No one disputes the physical facts of the blood pressure lowering effect of a portacaval shunt in the presence of portal hypertension but all insist upon a careful evaluation of the factors that establish the necessity of doing such an operation in an individual case of cirrhosis and when to do it.

Recent advances in the medical therapy of portal cirrhosis of the liver have established the fact that a percentage of these cases can be improved both clinically and by laboratory tests for the measure of liver function. The above facts automatically eliminate then all cases of cirrhosis for surgical consideration who have not had a thorough trial on the medical regime except those cases whose lives are threatened by hemorrhage and, even in the latter group, good judgment must be exercised as to the optimum time to operate. Whereas portal hypertension is the basic causal factor of hemorrhage in cirrhosis cases it is important to remember that a high prothrombin time, itself a sign of severe liver damage, may incite and prolong hemorrhage. Such cases are obviously poorer operative risks, but failing an energetic conservative regime, operation does offer a chance for life. Three of our eight cases fell into the above group. All three went through the shunt operation successfully but two of the three cases had a stormy convalescence. It is true that each case has had one bleeding episode over follow up periods of two years three months, one year and one year respectively, but in no instance was there vomiting of blood during these episodes as had occurred invariably before operation. Furthermore the post-operative bleeding episodes were limited to the passage of two or three tarry stools whereas before operation bleeding would persist for several

TABLE I—PROTEINS\*

Name	Age	Sex	Findings	Type of Shunt	Preoperative			Postoperative		
					TP	Alb	Glo	TP	Alb	Glo
1 Duncan	27	M	Cirrhosis Esophageal Varices	Spleno- renal	66	29	37	71	36	39
2 Boy 777262	16	F	Cirrhosis Esophageal Varices Ascites	Portal vein to Vena cava (Eck Fistula)	78 81	43 39	35 42	56 66	34 41	22 25
					80	41	39	61	38	24
3 Pahuci 690444	5	F	Cirrhosis Esophageal Varices Ascites	Spleno- renal	82	45	37	74 72 72	35 37 41	39 35 31
								73	38	35
4 Schein- garten 557450	28	M	Cirrhosis Esophageal Varices Ascites	Portal vein to Vena cava (Eck Fistula)	85	33	52	69 71 79 88	26 24 22 (15)	43 47 57 63
								62	22	47
								74		51
5 Cocozel 754188	42	M	Cirrhosis Esophageal Varices Ascites	Spleno- renal	75	35	4	62 68	25 26	37 42
								65	26	39
6 Mooney 536889	56	M	Cirrhosis Esophageal Varices Ascites	Spleno- renal	57 71	32 38	25 33	64 72	37 41	27 31
					64	35	29	58	31	27
								65	36	28
7 Long 783972	49	M	Cirrhosis Esophageal Varices Ascites	Portal vein to Vena cava	53	23	30	59 54	36 26	23 28
								57	31	26
8 Iacoletti 784905	58	M	Cirrhosis Esophageal Varices Ascites	Portal vein to Vena cava	52	29	23	45 49 47 50 50 62	25 23 29 19 20 30	20 24 20 31 30 32
								50	24	26

\* Proteins expressed in %

weeks. In fact in two of the three cases at the time of operation the patients had been bleeding for one month each and, in spite of transfusions, the hemoglobin wavered in the twenties in one and the low forties in the other.



Spleno-renal anastomoses using 6 and 8 mm tubes respectively were done in two of the three cases. In the third case a vein graft using the superficial femoral vein was used to join the portal vein to the vena cava. The objectionable use of a vein graft was necessary in this case on account of tissue edema. Because of the small size of the superficial femoral vein in comparison with the portal vein we feel that this particular shunt was capable of handling no more blood than the spleno-renal anastomoses performed in the other two cases. This was further borne out by the fact that the portal vein pressure fell to only 390 mm of water upon opening the anastomosis. We now know that all three of these cases should have had a shunt operation comparable to the full size of the portal vein—namely a direct end to side anastomosis of the portal vein to the vena cava. It is of interest that in a year's follow up on a fourth case of cirrhosis who preoperatively had bled less severely, there have been no postoperative bleeding episodes. In this case the portal vein was anastomosed end to side with the vena cava using a 12 mm vitallium tube. Furthermore x-rays of the esophageal varices done before and six months after operation revealed a marked reduction in the size of the varices postoperatively.

**Ascites** Excessive peritoneal fluid was found at operation in seven of the eight cases of cirrhosis followed postoperatively. There was no reaccumulation of fluid in three cases after operation. Two cases required paracentesis once and twice respectively. Whereas, in the remaining two cases paracenteses were performed over increasing intervals for a period of two months in one and perhaps five more months in the other.

A study of portal pressure readings taken at operation before and after opening the shunt when correlated with pre- and postoperative protein values, as these factors relate to the formation of ascites, would be highly informative. Unfortunately, often due to the exigencies of the operation, our portal pressure readings are far from complete. The protein values before and after operation in the eight cases of cirrhosis were as shown in Table I.

A summary of the protein values before and after the formation of portacaval shunts in eight cases of cirrhosis of the liver is as follows. In one case, having esophageal varices but no ascites, there was a significant rise in total proteins and albumin following operation. In two other cases there was a slight rise in total proteins and albumin follow-

TABLE II—BROMSULPHALEIN TEST  
Percentage of Dye Excreted After 30 Minutes

Name	Preoperative	Postoperative
Pahuci 690444	10%	5% 10% 8%
Duncan 767177	70%	38%
Cocozelo 754188	60% (S B 15 mg %)	65% (S B 25 mg %)
Box 777262	45%	10% 30% 20%
Scheingarten 557450	42%	40%
Mooney 536889	20% (S B 35 mg %)	22% (S B 10 mg %) 25% 35% 27%
Iacoletti 784905	35% (S B 4 mg %)	35% (S B 3 mg %) 20% (S B 3 mg %) 27% (S B 3 mg %) 61% No jaundice 55% No jaundice 39%

ing operation whereas in the remaining five cases there was a slight fall

The role of portal hypertension and low proteins as causal factors in the formation of ascites in cases of portal cirrhosis of the liver has long been known. Therefore the relief of ascites following the establishment of portacaval shunts in the above seven cases of cirrhosis having evidence of severe portal hypertension (esophageal varices) is not unexpected. The relative importance of the portal hypertensive factor in the cause and perpetuation of ascites is well demonstrated however in the five cases whose proteins failed to rise to preoperative levels following the establishment of portacaval shunts for the relief of portal hypertension. Whereas in all of the cases operated upon by us there was evidence of severe portal hypertension such is not the case in all cases of cirrhosis of the liver. There are some cases of cirrhosis with ascites due primarily to lowered proteins, a result of liver damage

in which the portal vein radicals have been relatively little constricted by fibrosis

Bromsulphalein liver function tests were performed before and after the establishment of portacaval shunts in seven of the eight cases of cirrhosis followed postoperatively (Table II)

A summary of the results of this liver function test is as follows. In four of the seven cases bromsulphalein retention decreased following operation, namely, 2 per cent, 32 per cent, 25 per cent and 2 per cent respectively. Whereas in three of the cases there was a slight rise in bromsulphalein following operation, namely 5 per cent, 7 per cent and 4 per cent respectively.

We realize that the number of cases is too small to make these findings of statistical significance, however, it so happened that in all three cases showing increased retention of bromsulphalein following operation jaundice was present when the tests were made—both before and after operation. All chemists familiar with the bromsulphalein liver function test are in agreement that the presence of an elevated serum bilirubin so complicates the quantitative determination of bromsulphalein in the blood as to vitiate the accuracy of the test. In view of the above facts then, should we discard the three cases in which the accuracy of the bromsulphalein tests was compromised by the presence of an elevated serum bilirubin, the evidence favors improvement in this liver function test following the establishment of portacaval shunts.

Unfortunately we cannot present an array of figures concerning other liver function tests before and after the establishment of portacaval shunts in these eight cases (Table III). The results were at least encouraging in the two cases having hippuric acid excretion tests before and after operation.

The behavior of the cephalin flocculation test is interesting.

The usual decrease in the prothrombin time following the establishment of portacaval shunts is informative to the extent to which the change may be attributable to improvement in liver function.

Two of the eight cases of cirrhosis followed postoperatively have died. One, the five year old child whose postoperative course was complicated by polycystic disease of the kidney and chronic nephritis, finally succumbed to uremia two years and three months following a spleno-renal anastomosis. At autopsy the splenic vein was found to have undergone fibrotic occlusion at the anastomosis site. This occurrence

TABLE III—HIPPURIC ACID LIVER FUNCTION TEST  
(Normal Secretion One or More Grams Per Hour)

<i>Name</i>	<i>Preoperative</i>	<i>Postoperative</i>
Long 783972	0.62 grams 1 hr	0.82 grams 1 hr
Scheingarten 557450	0.8 grams 1 hr	1.1 grams 1 hr 1.5 grams 1 hr 1.3

CEPHALIN FLOCCULATION TEST

	<i>Preoperative</i>	<i>Postoperative</i>
1	4+	0
2	3+	2+ 5 1.25+
3	4+	0
4	1+ 1+	0 0 0 0 0
5	3+	2+ 3+ 0 2+ 1.75+
Incoletti 784905	Negative	4+

PROTHROMBIN TIME

Those cases with elevated prothrombin times usually have returned to normal

in our first case was not altogether unexpected because it was noted at the completion of the operation that the splenic vein was sharply angulated over the edge of the vitallium tube. Our attempt to relieve this angulation by stay sutures was not essentially successful. The occurrence of angulation at the spleno-renal junction has been largely avoided in subsequent cases by mobilization of a longer segment of splenic vein. This can usually be done by the painstaking ligation of numerous pan-

creatic branches Even so in one case tissue edema was so extensive as to necessitate the use of a vein graft to bridge the space between the splenic and renal veins

Though complete fibrotic occlusion of the anastomosis was noted at autopsy no doctor familiar with this child's preoperative and postoperative course (and there were many) but would attest to her remarkable clinical improvement following operation Attempts at controlling an episode of bleeding that had recurred almost daily over a period in excess of a month had definitely proven a losing game in this child, until the situation of extremis was reversed following operation Considering the progressive improvement this child made over the year following operation in comparison with the steady downhill course during the year preceding operation is convincing evidence that the spleno-renal shunt was delivering a good volume of blood over the period And, it is my opinion that the fibrotic narrowing of the anastomosis progressed at a very slow rate with at no time the sudden intervention of thrombus Furthermore, there is no evidence of the latter upon careful examination of the specimen

Infra red photographs to show superficial collateral vessels on abdomen taken three weeks after and fourteen months after op would support the above conclusion

The second to die of the eight cases of cirrhosis followed operatively lived for one year following the establishment of a renal shunt This forty-two year old man had a very bad present illness going back months beginning with loss in weight and appetite, jaundice and ascites supervened There was a 4 plus cephalin flocculation test and a 4 plus A/G ratio Following the operation the man gradually gained strength and was finally able to work part time The ascites never recurred following hospitalization

Our last follow up on this patient was some time after the onset of his last illness We understand the illness was sudden with a fever and some abdominal discomfort He was sent to another hospital with a temperature of 104° F and a 4 plus cephalin flocculation test On the downhill, he became stuporous shortly after admission and a few days later was punctuated by an episode of hematemesis He recently received the pathological specimen in which the study of the liver The spleno-

found to be patent in the specimen though, due to the considerably larger renal vein, the walls were somewhat fluted bordering the junction with the splenic vein. However, union between the splenic and renal veins was firm. There was no thickening of the vein walls or other evidence of irritation by the vitallium tube. The intima was everywhere intact. No thrombus was present and within the vitallium tube there was full freedom of space for blood flow.

It is obvious from the specimen that the spleno-renal shunt in this case was capable of handling a considerable volume of blood though, no doubt, not nearly so much as an Eck fistula. It would appear from the high fever this man had upon entering the hospital that he may have had some kind of infection or toxemia. At any rate rapid failure of the liver, as no doubt this man had, can in a matter of a few hours so affect prothrombin as to constitute a tremendous factor in the inciting of hemorrhage in a patient proven to have esophageal varices. It is a matter of interest that our operative notes reveal this man's portal pressure as exceeding 500 mm. of water—the highest by 50 mm. of any case so far recorded by us. These facts would argue for the choice of Eck fistula (portal vein to veni cava) anastomosis in this man though it is unlikely that the difference would have been adequate to meet the onslaught of a rapidly mounting prothrombin time—a terminal event.

*Summary* A report of fourteen cases in which portacaval shunts were established was presented. The technique, indications for operation and the type of portacaval shunt to be employed were discussed. The role of the portacaval shunt in ameliorating the severity and frequency of hemorrhage in cases of portal hypertension was illustrated.

The influence of the portacaval shunt on ascites was emphasized.

Blood protein levels before and after the establishment of portacaval shunts in eight cases of cirrhosis of the liver were reported.

Bromsulphalein excretion figures before and after operation were presented. Finally, the effect of the portacaval shunt on hippuric acid excretion, cephalin flocculation and the prothrombin time in cases of cirrhosis was discussed.

✓ *Conclusions* The number of cases has been too small and the data accumulated insufficient to draw sweeping conclusions. Of one thing we are sure, however, and that is that unless the operation is carried out with infinite care as to details (and there are many) the chances of the portacaval shunt remaining patent are practically nil.

A REVIEW OF 401 CASES OF EARLY  
AMBULATION \*

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THIS paper is a discussion of 401 cases of early ambulation occurring at Presbyterian Hospital between September 1944 and July 1945. The method of handling these cases postoperatively is described and particular emphasis is placed upon the postoperative complications which occurred. The contraindications to early ambulation are briefly discussed and the series is compared with a similar group of cases, not ambulated, taken from the Surgical Files of 1943.

*Method* The general method of handling these cases is as follows:

As soon as the patient has fully recovered from the anesthesia, he is put up in a high gatch and encouraged to move about in bed and to take deep breaths. The next morning an abdominal binder is applied and the patient is allowed to stand beside the bed, remaining up about 15 minutes. That afternoon he is again allowed up and assisted in walking about the bed. The second day he is assisted to the bathroom and thereafter is allowed up and around as desired.

Each case is considered from the point of view of certain contraindications before the order for early ambulation is given. These contraindications fall into several groups. Prolonged preoperative bed rest, cachexia, cardiac insufficiency, recent coronary occlusion, shock, severe anemia, hemorrhage or fear of hemorrhage and the presence or suspected presence of thrombi or emboli make up the first group. Suppurative conditions such as peritonitis, pancreatitis and cholangitis make up the second group. Insecure anastomosis, copious tamponade and difficult hernial repairs in which the tissues available are of poor quality, form a third group. Simple drainage is not a contraindication to early ambulation, nor is the presence of a Miller-Abbott tube. In the final analysis the decision to allow the patient up is left to the surgeon who

\* This paper sponsored and discussed by Dr. Allen O. Whipple, Valentine Mott Professor of Surgery, College of Physicians and Surgeons, Columbia University on October 10, 1945 before the 18th Graduate Fortnight of The New York Academy of Medicine.

has done the case

*Data* There have been 401 cases of early ambulation at Presbyterian Hospital between September 1944 and July 1945. In this series 77.6 per cent of the cases were closed with silk, 10.2 per cent with gut and 12.2 per cent with cotton or other suture material. No particular type of abdominal incision has been favored. Fifty-eight per cent were walking by the end of the second P O day, 75 per cent by the end of the third P O day. The remainder were walking by the 5th P O day. The average length of stay in the hospital postoperatively was 11.3 days.

The types of cases, the average day up, the average duration of temperature, the average maximum temperature, the average length of stay P O, and the P O complications are given in Table I. Table II gives the occurrence and type of P O complications in a similar group of cases, not ambulated (taken from the surgical files of 1943). Table III summarizes the P O complications in the two groups.

Detailed review of the complications occurring in the early ambulation group is as follows:

*Pulmonary* There were eleven cases of bronchopneumonia, none severe. All eleven cases, however, were not ambulated until the fourth or fifth P O day. In every instance the pulmonary pathology and symptomatology disappeared rapidly as the patients were ambulated.

Two cases of atelectasis occurred within the first twenty-four hours after operation. Both were relieved by vigorous coughing and back-thumping. Neither case developed subsequent bronchopneumonia and both were ambulated on the third P O day.

*Vascular* There were 3 cases of phlebothrombosis. The first occurred in a patient convalescing after a herniorrhaphy. He was ambulated on the fifth P O day and on the eighth P O day had a fully developed phlebothrombosis in one leg. He was put back to bed and made an uneventful recovery.

The second was in a case of acute appendicitis, ambulatory on the first P O day and discharged on the fifth P O day. Two days later he returned with bilateral phlebothrombosis and x-ray evidence of a pulmonary infarct. Bilateral vein ligation was performed and the patient subsequently recovered.

The third case developed phlebothrombosis eighteen days after a resection of the large bowel for carcinoma. This patient had been



TABLE I—ANNUAL GROUP

Types of Cases	No	Average Day Up	Average Length of Stay P.O.	Average Duration of Temp (Days)	Average Maximum Temp	COMPLICATIONS				
						Broncho-pneumonia	Atelectasis	Plebo-thrombosis	Pulmonary Infarct	Calhernization
Gall Bladder & Common Duct	68	21	13	38	101.4	3	0	0	0	1
Appendicectomy	114	18	6.6	12	100.2	0	0	1	1	1
Herniae	95									
a One side	65									
b Bilateral	18	15	9.9	23	100.5	0	0	1	0	2
c Recurrent	4									
d 1 pigstic	8									
Partial Gastrectomy	23	32	12.9	39	101.5	2	2	0	0	0
Hydrocectomy										
a Toxic	15	29	6.1	23	100.9	1	0	0	0	0
b Non-toxic nodular	22	18	5.2	2	100.5					
Ridicil Neck & Bicus	1	35	9	17	100.7	0	0	0	0	0
Exploratory Celiotomy	15	27	13	31	101.3	1	0	0	0	0
Volvulus of Sigmoid	2	10	10	0	98.6	0	0	0	0	0
Hysterectomy	2	25	10	8	102.2	0	0	0	0	0
Pancreatotomy	2	3	25	11	102.6	0	0	0	0	0
Splenectomy	2	1	11	2	101.2	0	0	0	0	0
Carcinoma of Large Bowel	9	3	16	5	102.4	0	0	1	0	0
General	28	36	13	25	101.2	1	0	0	0	9
Total	101	24	11.5	35	101.1	11	2	3	1	16

TABLE II  
NON-AMBULATORY GROUP

		COMPLICATIONS					
<i>Types of Cases</i>	<i>No</i>	<i>Broncho- pneumonia</i>	<i>Atelec- tasis</i>	<i>Phlebo- thrombosis</i>	<i>Pulmonary Infarct</i>	<i>Dis- tention</i>	<i>Catheri- zation</i>
Gall Bladder & Common Duct	65	5	1	2	1	2	0
Appendectomy	114	3	2	2	1	2	1
Hernia	95	6	1	3	1	0	7
Partial Gastrectomy	23	2	2	0	0	0	2
Thyroidectomy	37	1	0	0	0	0	0
Radical Neck and Breast	4	0	0	0	0	0	2
Exploratory Celiotomy	15	0	0	1	0	0	1
Tvolvulus of Sigmoid	2	0	0	0	0	0	0
Hysterectomy	2	0	0	0	0	0	0
Pancreatotomy	2	0	0	1	1	0	0
Splenectomy	2	0	0	0	0	0	0
Carcinoma of Large Bowel	9	0	0	1	1	1	0
General	28	26	0	1	0	13	2
<i>Total</i>	401	23	6	11	5	18	16

TABLE III

		COMPLICATIONS											
		Broncho- pneumonia		Atelec- tasis		Phlebo- thrombosis		Pulmonary Infarct		Dis- tention		Catheri- zation	
	No	No	%	No	%	No	%	No	%	No	%	No	%
Ambulation Cases	401	11	2.7%	2	5%	3	7%	1	2%	0	0%	16	4%
Not Ambulated	401	23	5.7%	6	1.5%	11	2.7%	5	1.2%	18	4.4%	16	4%

## COMBINED PENICILLIN AND HEPARIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS\*

*Progress Report of the First Seven Consecutive Successfully  
Treated Patients*

LEO LOEWE, PHILIP ROSENBLATT, HARRY J. GREENE

THE results following the combined use of penicillin and heparin in the treatment of subacute bacterial endocarditis have been published previously,<sup>1 2 3,4</sup> the response to the conjoint therapy being noted initially in seven consecutive, unselected patients suffering from the disease. The original report<sup>1</sup> stated "Further observations will be required to determine the permanence of results, but the immediate effects suggest uniformly successful sterilization of the blood and relief of clinical manifestations." We now record the follow-up data (Table 1) of the initial series of seven patients whose progress has justified the earlier evaluation.

### COMMENT

Seven consecutive, unselected patients with subacute bacterial endocarditis were treated by the combination of penicillin and heparin. In each instance the outcome seemed signally successful, the blood cultures became sterile and the symptoms of fever and toxemia abated.

The present report is in the nature of a follow-up review after a post-therapy interval that approximates two years. In this interim one of the patients died due to intractable congestive heart failure. An autopsy could not be obtained but the patient had shown no signs of bacterial activity for at least six months prior to death. A second patient is still incapacitated as the result of protracted heart failure. She was hospitalized for this and complicating rheumatic activity. Repeated blood cultures were negative. The rheumatic activity subsided with salicylates and bed rest but she was discharged with residual manifesta-

\* From the Department of Medicine and the Department of Laboratories, Jewish Hospital of Brooklyn.

# COMBINED PENICILLIN-HEPARIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS Progress Report of First Seven Consecutive Successfully Treated Patients

Patient Number	Age	Infecting Organism	Span of Treatment	Penicillin Total Of Units	Heparin Mls	Months Post Therapy	Follow-Up Notes
1 I I	7 1/2	Pneumococcus type 27	6/19 to 7/5/43	867,920	1200	28	9/15/43 Hgb 90%, RBC 5,200,000, ESR 12 mm/hr Blood culture sterile on this date and again on 2/24/44 and 5/23/44 Upper respiratory infection tonsillectomy, adenoidectomy and measles without recurrence 6/1/45 Weight 110 lbs., slight exertional dyspnea, otherwise normal activity Attending school 10/21/45 No complaints Engaging in all routine activities including sports without ill effects
2 S R	31	Streptococcus viridans	6/19 to 11/2/43	7,890,000	7100	24	2/11/45 Weight 183 lbs Hgb 94%, ESR 2 mm/hr Hrs had two virus infections, upper respiratory type, for which sulfonamides were given prophylactically Left ventricular enlargement of heart by x ray LCG shows left axis deviation 6/3/45 Slight exertional dyspnea Blood culture sterile Hgb 101%, ESR 2 mm/hr Working eight or more hours a day for nine months and retail hardware salesman 10/21/45 Condition status quo Weight 183 lbs, B P 142/72 Hgb 97%, LSR 6 mm/hr Blood culture sterile
3 I O	24	Streptococcus viridans	7/11 to 10/19/43	7,694,800	6700	--	Moderate congestive heart failure soon after discharge Exertional dyspnea and dependent edema increased despite therapy Readmitted to hospital 1/1/44 to 2/12/44 Succumbed to intractable congestive heart failure resulting from inability of myocardium to accommodate for loss of valve substance No clinical or laboratory signs of bacterial activity for six months prior to death
4 I N	31	Streptococcus viridans	8/26 to 9/8/44	1,400,000	1800	25	1/2/44 Chilling of fingers receded No residual from post therapy cerebral embolism Hgb 80% LSR 5 mm/hr and blood culture negative 2/11/45 Weight 176 lbs No visible change in either size or contour of heart by x ray as compared with study of August 1943 6/3/45 No complaints Hgb 101%, LSR 3 mm/hr Blood culture negative 10/21/45 Occasional colds No complaints Weight 189 lbs, B P 180/60, Hgb 97%, LSR 2 mm/hr Blood culture sterile
5 C M	22	Streptococcus viridans	8/26 to 10/19/44	6,650,000	7600	24	Developed congestive heart failure following excessive exertion 6/17/44 readmitted to hospital for intensive treatment of myocardial insufficiency and superimposed rheumatic activity Ten percutaneous and fracture joint pain, arrhythmic fibrillation Reported blood culture sterile Responded slowly to salicylates and deliriant therapy Discharged with residual heart failure 2/11/45 Electrocardiogram shows no change in cardiac silhouette since initial discharge from hospital LCG discloses arrhythmic fibrillation, myocardial damage and right axis deviation 6/29/45 Left much better following continuous regime for protracted heart failure Less dyspnea and fatigue billy Abdomen less distended some recession of liver enlargement and minimal peripheral edema 10/21/45 Progressive improvement Now maintained on urea obscurum necessary for incertum diuresis Weight 122 1/2 lbs, B P 98/64 Hgb 97%, LSR 28 mm/hr Blood culture sterile
6 H C	52	Streptococcus lactolyticus	8/28 to 9/10/43	1,400,000	1500	25	11/21/44 Weight 163 lbs Hgb 94% LSR 7 mm/hr Blood culture sterile 2/11/45 No complaints, exertional dyspnea or fragility Aortic diastolic murmur softer in character ECG shows left axis deviation and myocardial damage No clinical evidence of myocardial embarrasment 6/3/45 Some fragility Occasional precordial distress No changes clinically B P 138/90 Blood culture negative Employed for over a year as secretary 10/21/45 No complaints No edema Weight 156 1/2 lbs, B P 138/84, Hgb 90%, LSR 11 mm/hr Blood culture sterile
7 I S	15	Streptococcus viridans	9/26 to 10/9/43	1,204,200	6700	24	2/11/45 Progressive improvement States he feels better than prior to illness Mitral systolic murmur barely audible Cardiac x ray fails to show definite evidence of cardiac enlargement contour was not disturbed LCG discloses sinus tachycardia and left axis deviation 6/3/45 No exertional dyspnea even on climbing three flights of stairs Weight 192 1/2 lbs An-cultatory findings unchanged Hgb 106%, ESR 11 mm/hr Blood culture negative Army rejection only on basis of poor vision Working steadily as machine operator (10/21/45)

tions of myocardial embarrassment. There has since been slow but progressive response to treatment.

The remaining five patients have been completely rehabilitated, the youngest, a child of nine, is attending school. Of the four adults, one is working as a retail salesman, another as a waiter in a night club, a third as secretary, and the fourth as a machine operator.

During this post-treatment period, several of the patients have had upper respiratory infections without activation of the endocarditis. Patient No. 1 has successfully survived the measles, a severe tonsillitis, tonsillectomy and adenoidectomy. Patient No. 7 was rejected in his Army physical examination merely on the basis of poor vision. His present work as a machine operator requires that he climb daily three flights of stairs.

#### SUMMARY

A post-treatment observation period approximating two years relative to the original seven patients treated for subacute bacterial endocarditis by combined penicillin and heparin therapy justifies the conclusion that the immediate effects of successful sterilization of the blood and the relief of clinical manifestations have been maintained. Observation of this initial group will be continued and later reports may further indicate the relative permanence of the successful therapeutic result.

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## *Postwar Expansion of Senior House Staff Positions in the Mount Sinai Hospital*

I SNAPPER

Director Medical Education The Mount Sinai Hospital

The problems of medical education connected with the return of many thousands of Army and Navy Medical Officers to civilian life are manifold. The greater part of these men desire postgraduate training. Many are interested in postgraduate lecture courses, others wish to work for a period of one or more months as postgraduate students in different departments. As far as the capacity of the hospital permits it usually is not difficult to cope with such wishes.

One of the major problems is presented by the desire of hundreds of returning Medical Officers to receive supplementary hospital training as assistant residents and residents. Most of these men have been obliged to join the Armed Forces after 9-month or 12-month periods of internship and it can be readily understood that they feel the necessity to complete their house staff training. In addition, large numbers of Medical Officers had already decided before they went into the Army or Navy to specialize in medicine or surgery. Often they had started their specialized training before the war and now after discharge from the Service they try to obtain residencies in the specialties in which they are interested. Finally, there are many Medical Officers who have already worked as general practitioners for one or more years and who, during their military career, have decided to go in for specialties.

The Trustees of the Mount Sinai Hospital felt it imperative to cope as much as possible with the needs of the returning Medical Officers. This decision required the institution of new assistant residencies and residencies. In order to obtain the necessary expansion of the house staff, several difficulties had to be overcome. In the beginning it even seemed that these plans could not be

realized because of limitation of house staff quarters and dining room facilities. However, by the introduction of certain improvisations and reorganizations a considerable increase of both house staff quarters and dining room facilities could be obtained. Thereafter, it was possible to submit the following plans which ultimately were accepted for implementation.

1 All pre-existing Assistant Residencies and Residencies are to be filled by returning Medical Officers as soon as the positions become free. After April 1, 1946, practically all pre-existing Assistant Residencies and Residencies will be occupied by returning Medical Veterans.

### 2 Creation of new Residencies a *Medicine*

(1) The Mount Sinai Hospital has two Medical Services, each of which had one Resident. As of January 1, 1946, the house staff of each Service will be headed by two Residents.

(2) The Mount Sinai Hospital had under wartime conditions 8 senior interns who served a mixed internship. By April 1, 1946, these mixed senior internships have been abolished. Six of these 8 senior interns will be replaced by Assistant Residents in Medicine who will serve for 8 months in General Medicine, 2 months in Neurology and 2 months in Pediatrics.

(3) The Mount Sinai Hospital always had 2 Medical Resident Physicians in the Semi-Private and Private Pavilions. On January 1, 1946, this number was increased to 6. Each of these 6 men will work for 8 months in the Private Pavilions and for 4 months in the medical wards of the hospital. During the latter period each will act as the third assistant Resident in the Medical Wards, which will bring his training under

the direct supervision of the medical chiefs

Four Resident physicians are sufficient to handle the work connected with the medical patients in the Semi-Private and Private Pavilions. When 4 Residents are on duty, enough time is available to permit them to attend medical lectures and other educational activities which are going on daily in the Hospital, usually between 4 and 6 P.M. Measures are taken in order to obtain a closer supervision of the work of the Medical Residents in the Private and Semi-Private Pavilions by the Attending Staff members whose patients were admitted.

*b Pediatrics, Orthopedics, Ophthalmology, Pathology, Neurology and Radiology*

In addition to the normal number of pre-war Residencies, an extra one-year Assistant Residency was created in Pediatrics, in Orthopedics, in Ophthalmology and in Pathology. The Department of Neurology opened two new Assistant Residencies, the Department of Radiology two new Residencies and three positions for Postgraduate students.

*c Neurosurgery and Urology*

Measures were taken permitting the creation of a new Residency in Neurosurgery and a new Assistant Residency and Residency in Urology which had not existed under pre-war conditions.

*d Pathology*

The number of Residents in Pathology was increased from 2 to 3. Apart from the regular Residents, the Department of Pathology has always had a considerable number (about 10) of Fellows and Research Assistants. These positions are from now on reserved for returning Medical Officers and within a year these positions will all be held by Veterans who will be trained as Postgraduate students.

*e Surgery*

Instead of the senior interns who, during wartime rotated through the surgical services, two new positions of junior assistant residents are created. These men will rotate through General Surgery, Urology (6 weeks), Orthopedics (4 weeks), and Gynecology (6 weeks).

The Mount Sinai Hospital had two Assistant Residents and two Residents in the Surgical Wards containing around 120 beds.

The Surgical Chiefs were of the opinion that an increase in this number would lead to an undesirable dilution of the operating activities of the Residents. It followed that an increase of the surgical resident training in the Mount Sinai Hospital could only be obtained by a reorganization of the Surgical Assistant Residency and Residency in the Semi-Private and Private Pavilions. On an average, there are 150 surgical patients in the Semi-Private and Private Pavilions of the Hospital. Surgical Residencies in the Private and Semi-Private Pavilions have certain innate deficiencies which can partly be remedied but can never be cured entirely. The main objection against such a Residency consists of the fact that Surgical Residents in the Private Pavilions cannot be allowed to perform independently surgical interventions. The practical work of such Residents can, therefore, at best consist only of assisting expert surgeons at operations.

Notwithstanding this deficiency it has been possible to remodel the Surgical Residencies in the Private Pavilions in such a way that a year of intense and fruitful instruction in surgery resulted. In per centime, the number of Assistant Residents and Residents in Surgery in the Private Pavilions varied from 6 to 8. It was decided to increase this number to 18 Resident Surgeons, 9 of these are to be appointed every January 1st, the second group of 9 every July 1st. During the first 6 months of their appointment these resident surgeons will work as Assistant Residents, the second half-year as Residents. In order to streamline the work of the Surgical Assistant Residents and Residents, the considerable number of operating surgeons who admit patients to these pavilions was divided into 6 groups.

Three of these groups consist each of an Attending Surgeon of the Mount Sinai Hospital with his Associate. The 4th group consists of the Chief Gynecologist with 3 of his colleagues and Associates.

The 5th group consists of the Attending Urologist with one Associate.

The 6th group designated as 'The Pool' is formed by all the other surgeons who operate in the Private and Semi-Private Pa-

TABLE I

POSIWAR INCREASE OF ASSISTANT RESIDENCIES AND  
RESIDENCIES OF THE MOUNT SINAI HOSPITAL

	ASSISTANT RESIDENTS		RESIDENTS	
	Peacetime	Postwar	Peacetime	Postwar
Gynecology	1	1	1	1
Medicine (wards)	0	6	2	4
Medicine (private)			2	6
Neurology	2	5	1	1
Ophthalmology	1	2	1	1
Orthopedics	1	2	1	1
E N T	1	1	1	1
Pathology			2	3
Pediatrics	2	3	1	1
Radiology			4	6
Surgery (ward)	2	2	2	2
Surgery (private)	4	9	4	9
Urology		1		1
Neurosurgery				1
Anesthesiology			2	2
	—	—	—	—
	14	32	24	40

vilions

To each of the first 3 groups mentioned above, one Assistant Resident and one Resident are assigned. One Assistant Resident is assigned to the gynecological group, another Assistant Resident to the urological group. To the pool 3 Residents and 3 Assistant Residents are assigned. The Assistant Residents and Residents make daily rounds with the surgeons to whom they are assigned, assist at the operations of these surgeons and take care of the after treatment of the patients.

The one remaining Assistant Resident works as an Assistant Resident in the Department of Urology of the Hospital. The 3 remaining Residents work as Assistant Residents in the Wards because at the same time the regular peacetime Assistant Residencies in the Wards have been abolished.

The schedule divides the year into 6 periods of 2 months each. Each of the as-

signments mentioned above lasts for 2 months. Each man works one period of 2 months as Assistant Resident in the Wards, works for 2 periods of 2 months each in the Pool. For the remaining 3 periods of 2 months each, he is assigned either as an Assistant Resident or Resident to one of the first 3 groups or as an Assistant Resident to the Gynecologists or the Urologists or as an Assistant Resident to the Urological Wards.

For the returned Army Veterans who work as House Staff Members or Postgraduate students, a teaching program has been organized.

1 Every day between 4 and 6 P M, Surgical, Orthopedic, Neurosurgical, Urological, Gynecological and other demonstrations and lectures are held. The resident group is assigned to be present at the monthly Surgical Departmental Conference, the Urological Conference, the Gynecological Con-



ference, etc. They also attend the Clinical Pathological Conferences which are held once or twice a week in the Hospital.

2 A special weekly X-ray conference for the Semi-Private and Private Pavilions has been created. Here the Residents present a short clinical resume of the case history of their patients, whereafter the Radiologist discusses the X-ray films taken of the patients.

3 A special weekly Surgical Pathological Conference for the Semi-Private and Private Pavilions has been organized where the surgical specimens obtained during the week in these pavilions are demonstrated and discussed by the Pathologist.

4 Each surgical Resident and each Assistant Resident has to follow one evening a week for 2 hours a course in Surgical Pathology where, after demonstration of the microscopic specimens by an instructor, the Residents, themselves, study these specimens under the microscopes under supervision.

5 Finally, Columbia University has placed one dissection room and 2 bodies at the disposal of the Mount Sinai Hospital where each Assistant Resident and Resident follows a course in practical dissection under strict supervision by an expert instructor in anatomy 2 evenings per week for 4 months.

In this way the Surgical Residency in the Semi-Private and Private Pavilions has been transformed to a year of careful and intensive training in Surgery. This year Residency offers not only well supervised observation and surgical diagnosis at the bedside with daily assistance at operations, but also basic medical training in Anatomy, Surgical Pathology and X-ray diagnosis. The practical training is rounded up by daily clinical demonstrations and discussions of surgical and allied problems.

It seems fair to weigh the advantages and disadvantages of such a Surgical Residency in the Semi-Private and Private Pavilions as compared with a Residency in the Surgical Wards of the Hospital.

The main disadvantage that a Resident in the Private Pavilions is not in a position to perform independently any kind of major surgery, can never be entirely overcome. In the schedule described this de-

ficiency is at least partly remedied because every Resident in the Private Pavilion works for a period of 2 months as an Assistant Resident in the Surgical Wards of the Hospital. This period always falls in the second part of the assignment when the Private Surgical Resident has already obtained a certain amount of experience. It will thus be possible to assign him during this two-month sojourn in the Wards a certain amount of independent surgery.

Three of each group of 9 men will, in addition to this two-month Assistant Residency in the Surgical Wards, also work for 2 months as an Assistant Resident in the Urological Wards.

The Residency in the Private Pavilions, however, has not *only* disadvantages. As a matter of fact, it has major advantages. In this connection the more intimate participation of the Private Resident in the work of the Surgical Chief may be mentioned. The Attending Surgeons, although well acquainted with the medical and surgical problems of all their ward patients, actually perform only a limited number of operations on ward patients. Part of the technical work in the Surgical wards is assigned to Associate Surgeons and Adjunct Surgeons. The Ward Residents, therefore, receive the major part of their technical training from the younger Surgical Staff members and have only relatively little direct contact with the Chiefs. In the Private Pavilions the Surgical Chiefs perform all the operations upon their patients personally. Since each Attending Surgeon has about 15-20 patients in the Private and Semi-Private Pavilions, the personal teaching of the Assistant Resident and Resident in the Private Pavilions by the Surgical Chief himself is much more intensive than in the Ward.

Another point has also to be considered. In the Hospital Wards the Surgical Chiefs perform only the more complicated interventions. The Ward Resident, therefore, learns the technique of hernia,—appendix,—simple gall bladder,—simple stomach operations—from the younger Attending Surgeons. In the Private Pavilions conditions are different and the Residents in the Private Pavilions are instructed in the tech-

nique of all operations—simple and complicated—by the Chiefs themselves

Finally, the amount of medically useless activities which the Hospital Administration requires of Ward Residents has in the course of years reached colossal dimensions. This results in a considerable amount of loss of time to the Ward Residents. It is well-nigh impossible for the Ward Residents to be present at the educational functions of the Hospital unless these are organized at night. The Ward Residents would not be in a position to follow the courses of instruction outlined above as organized for the Residents in the Private Pavilions.

The Residency in the Private Pavilions, therefore, offers valuable training in clinical and operative surgery and in the basic medical sciences and suits exactly the needs of the returning Medical Officers and forms

an excellent preparation for further specialization in Surgery. It is to be foreseen that in the future the Mount Sinai Hospital may well require such a year Residency in the Private Pavilions as a prerequisite for Ward Residencies in Surgery, Urology, Gynecology, and Orthopedics.

In this way the number of assistant residencies has been increased from 14 to 32, of residencies from 26 to 40. In addition to this creation of 32 new positions on the House Staff, the reorganization of the medical and surgical residencies in the Semi-Private and Private Pavilions has transformed the former 2 medical and 8 surgical residencies in these Pavilions into educationally valuable assignments.

The factual increase, therefore, amounts to 42 senior House Staff positions.

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- Year Book of Radiology, 1945
- Year Book of Urology, 1945

## CORRECTION

The Director, Board for the Investigation of Epidemic Diseases, Army Service Forces advises the Editor that the military title, Major MC, erroneously appeared under the name of C H Rammelkamp in the Bulletin, Vol. 21, No 12, p 656 1945

BULLETIN OF THE NEW YORK  
ACADEMY OF MEDICINE

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BULLETIN OF  
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OF MEDICINE



JUNE 1946

FACTORS COMMON TO SURGICAL  
LESIONS OF THE BILIARY TRACT

ALLEN O WHIPPLE\*

I am introducing the symposium dealing with the treatment of several of the important lesions of the biliary tract it is my duty to call attention to the three factors that determine the pathogenesis of every lesion of the biliary tract requiring surgical therapy. These factors are, first, disturbed metabolism of cholesterol and salts of the bile acids resulting in gallstone formation—this may be named factor M. Secondly is the factor of infection or inflammation, spoken of as I. The third factor is obstruction, or factor O. Singly or in combination one or more of these factors is present in the pathogenesis of every lesion of the biliary tract requiring surgery.

A knowledge of these factors and the location of them in the different parts of the biliary tree is of the greatest help in the diagnosis of the lesions, in determining the indications for therapy, in following the postoperative course of the patient, in treating the complications and in giving the prognosis after operation.

As an example. A patient with a history of repeated attacks of biliary colic without jaundice is seized with severe right upper quadrant

\* From the Department of Surgery, Columbia Presbyterian Medical Center, New York, N. Y.  
Read at Symposium on Biliary Tract Surgery, Section of Surgery, The New York Academy of Medicine, February 1, 1946.

pain followed by extreme tenderness over a palpable mass in the region of the gall bladder. Factors M and I can be considered present and limited to the gall bladder. Cholecystectomy is indicated. An acutely inflamed gall bladder containing a single large stone is removed. The patient has a smooth postoperative course without jaundice and with normal bowel movements. The factors M and I have been removed. Factor O was not present.

Another example. A patient, 52 years old, with no history of previous attacks of pain develops a gradually increasing jaundice and acholic stools. A large pear-shaped gall bladder develops in the right upper quadrant. The diagnosis of a carcinoma of the bile duct or ampullar region below the cystic duct with factor O as the single factor in the pathogenesis of the disease is obvious. If at operation the gall bladder only is drained, factor O is still present and the biliary fistula will persist. Thus the prognosis is determined by evaluating factor O.

For the medical student as well as the practitioner a clear understanding of these factors in relation to pathogenesis, diagnosis, operative indications and procedure, postoperative course and late prognosis in biliary tract disease requiring surgery is essential. Attention to these factors and their location in the biliary tree makes the study of bile tract disease interesting, the therapy sound and the prognosis accurate.

THE SURGICAL TREATMENT OF  
ACUTE CHOLECYSTITIS\**Introductory Remarks*

GEORGE J HEUER

Chief of Surgery New York Hospital

I T WAS, I think, in 1910 or 1911 that a private patient of Dr Halsted was admitted to the Johns Hopkins Hospital with the symptoms and signs of acute cholecystitis. I saw the patient with Dr Halsted. He decided to operate, and so as soon as the patient was properly prepared she was taken to the operating room. I assisted Dr Halsted at the operation.

The gall bladder was large and acutely inflamed and the omentum was loosely adherent to it. Without hesitation and without comment to indicate that he was doing something unusual he proceeded to do a cholecystectomy. It was the first cholecystectomy I had seen for acute cholecystitis. I was struck by the smooth convalescence of the patient and the case made a great impression upon me.

At the time, cholecystostomy with drainage was practically the universal treatment for gall stone disease of the gall bladder, and the deliberate attack upon the gall bladder in the acute phase of acute cholecystitis was rare indeed. When in 1922 I went to Cincinnati, I found again that operation for acute cholecystitis was not practiced, the acute process being allowed to subside, and if and when it did subside, cholecystostomy was commonly done although cholecystectomy was being discussed and practiced.

I had a good opportunity in Cincinnati to observe the course of acute cholecystitis under a waiting policy. I have to admit that I observed the gall bladder perforate while the patient was in the hospital, and that I saw not only extracholecystic localized abscess but generalized peritonitis supervene. I also observed that the gall bladder in acute

\* Read before the Section of Surgery of The New York Academy of Medicine 1 February 1946.  
From the Department of Surgery of The New York Hospital and Cornell University Medical College.



cholecystitis may proceed in its pathological course to gangrene and perforation in the presence of subsiding and minimal signs and symptoms. Such observations led me to operate more frequently and to encourage my resident staff to operate in the acute phase of the disease, and before I left Cincinnati to come to New York I had decided that early operation in acute cholecystitis was the surgical treatment of choice.

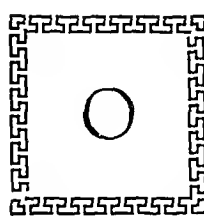
Early operation in this disease was then established by me as a policy to be followed by my staff on my ward service at the New York Hospital, and it has consistently been followed since September, 1932. Dr. Glenn will tell you the results of such a consistent policy.

---

## THE SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS

FRANK GLENN

Associate Professor of Clinical Surgery, Cornell Medical College

 OVER a period of thirteen years, from September 1, 1932, to September 1, 1945, a total of 527 patients with acute cholecystitis were operated upon in the New York Hospital. There were thirteen deaths—a mortality rate of 2.46 per cent. It is the purpose of this discussion to present our definition of the surgical treatment for cholecystitis and to elaborate in some detail the operative procedures that are commonly employed. In the discussion of these operations the indications and contraindications for each procedure are reviewed and the resulting complications discussed.

By the surgical treatment of acute cholecystitis we mean operating upon the patient when adequately prepared unless there is some contraindication that is not immediately reparable. The gall bladder has been removed in 460 patients, or 87.4 per cent of those subjected to operation, and cholecystostomy was performed in sixty-seven cases, or 12.6 per

cent The additional procedure of exploration of the common duct has been limited to those in which indications were definite, and these totalled 47, or 8.9 per cent The policy has been adhered to that the welfare of the patient is continually kept in mind and that the operative procedure employed has been one of the greatest possible benefit and least hazard The operation is not decided upon entirely before the procedure is undertaken For instance, if during operation a cholecystostomy seems to be the procedure of choice, a cholecystectomy is abandoned

## ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL

September 1, 1932, to September 1, 1945

Total cases	527
Deaths	13
Mortality	2.46%
<i>Operative Procedures</i>	
Cholecystectomy	460
Cholecystostomy	67
	(12.6% of total operations)
Common Duct Exploration	43

Cholecystostomy was performed in 67 instances and was followed by 5 deaths This procedure is clearly indicated under certain circumstances, as when the patient is too ill to withstand cholecystectomy or when cholecystectomy presents too great difficulties For the extremely debilitated patient or for the very ill, we doubt if there are any contraindications for cholecystostomy because it may be done under local anesthesia, disturbing the patient very little, and at the same time the simple procedure may be a life-saving one The decompression of the biliary tract averts catastrophe by preventing progressive liver damage if complete biliary obstruction is present

In determining the type of operation to be done, the gross appearance of the presenting pathological changes is of importance In the first place, if there is gangrene and perforation with accompanying generalized peritonitis, simple drainage of the abdomen together with cholecystostomy is indicated If there is gangrene and perforation which has resulted in localized peritonitis or abscess in the region of the extra-hepatic portion of the gall bladder, then one may choose between cholecystectomy and cholecystostomy However, in the presence of ex-

tensive adhesions of omentum to the gall bladder and into the biliary fossa, it is indeed questionable whether these should be disturbed and a cholecystectomy done. If the patient is unusually ill and if postoperative complications appear in the offing, then certainly cholecystectomy should not be attempted. Perforation of the gall bladder with a small abscess or perforation into the adjacent liver tissue is no contraindication to cholecystectomy. The patients with simple acute cholecystitis are in general best treated by cholecystectomy.

Common duct exploration in acute cholecystitis has been limited in our clinic to those patients with unequivocal indication of common duct obstruction. If this exists, common duct exploration should be undertaken even though it adds additional risk to the procedure. The incidence of postoperative complications is in this series apparently increased. At the same time it may be said that these patients are usually in the group that is more seriously ill. For the extremely ill, jaundiced patient, decompression (that is, cholecystostomy) may be utilized as a compromise procedure, having in mind, of course, following the subsidence of jaundice, the exploration of the common duct with the patient in a greatly improved condition.

The presence of jaundice requires the determination of blood prothrombin and the evaluation of any bleeding tendency, and in the presence of acute disease time may not be afforded for this. For such patients the use of whole blood transfusions and parenteral administration of Vitamin K may prevent serious postoperative hemorrhage.

The common duct was explored in 47 of these patients, an incidence of 89 per cent. Stones were recovered in 29 of these, or 61.7 per cent. It is probable that the opening of the common duct in the patient without stones does not materially increase the postoperative complications. On the other hand, failure to remove common duct stones may lead to catastrophe. Therefore, when the surgeon is unable to conclude definitely whether or not there are stones, it may be better judgment to open the common duct.

The operation of choice in acute cholecystitis is cholecystectomy. The removal of the gall bladder interrupts the pathological process and averts the danger of gangrene and perforation. This procedure is sometimes contraindicated because of (1) the presence of peritonitis due to perforation of the gall bladder. In this situation an extensive operation is contraindicated because of the gravity of the patient's condition.

(2) Conditions which make it difficult to identify the important structures in the biliary fossa. When the gall bladder is greatly distended and adherent, the adjacent viscera may be so distorted that anatomic relationships are obscured. In this situation there is danger of inadvertently injuring the hepatic vessels or the common duct. (3) The presence of a severe jaundice caused by obstruction in the common duct is a contraindication to an extensive operative procedure. It is usually better to drain the gall bladder and thereby relieve the jaundice than to subject the patient to removal of the stone from the common duct. (4) In a patient whose general condition is so grave that a general anesthetic and prolonged operation are not justified. This state of affairs is likely to arise when the cholecystitis is superimposed upon systemic disorders, such as hypertension or cardiovascular and renal disease. In such cases a compromise must be sought in the form of surgical treatment which, without adding to his burden, tides the patient over the immediate crises.

## ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL

September 1, 1932, to September 1, 1945

*Patients Fifty Years of Age or Over*

Total	175
Deaths	9
Mortality	5.14%

*Operative Procedures*

Cholecystectomy	140
Cholecystostomy	35
	(20% of total operations)
Common Duct Exploration	22

In the series of 527 patients treated surgically 175 were fifty years of age or over. There were nine deaths, or a mortality rate of 5.14 per cent. One hundred forty were subjected to cholecystectomy. Thirty-five, or 20 per cent of the 175, were treated by cholecystostomy. Twenty-two had in addition to these operations exploration of the common duct. The mortality rate of 5.14 per cent of these patients who were fifty years of age and over indicates the definitely greater risk associated with them than those of less than fifty years of age with a mortality rate of 1.13 per cent. The following chart with an analysis of the nine deaths demonstrates the complications that terminated fatally.

In the consideration of this group of deaths it may be of significance

## SUMMARY OF RESULTS AFTER OPERATION

<i>Sex</i>	<i>Age</i>	<i>History of Biliary Disease In Years</i>	<i>Duration of Attack</i>	<i>Jaundice</i>	<i>Findings</i>	<i>Operation</i>	<i>Cause of Death</i>
1	F	8 plus	3 days	+	Acute cholecystitis with perforation, peritonitis	Cholecystectomy with drainage	Peritonitis
2	F	4 plus	7 days	0	Acute cholecystitis with gangrene	Cholecystostomy	Peritonitis, bacteremia
3	F	20 plus	10 days	+	Acute cholecystitis, cholelithiasis, common duct obstruction	Cholecystostomy	Bacteremia, stone in common duct, thrombosis hepatic artery
4	M	7 plus	8 days	+	Acute cholecystitis, cholelithiasis	Cholecystostomy	Hepatic failure, biliary cirrhosis
5	F	Inadequate history	4 days	0	Acute cholecystitis, cholelithiasis	Cholecystectomy, drainage abscess	Subhepatic abscess*
6	F	12 plus	8 hours	0	Acute cholecystitis, cholelithiasis	Cholecystectomy	Coronary occlusion, cardiac failure
7	F	2 plus	2 days	+	Acute cholecystitis	Cholecystectomy with drainage	Adrenal insufficiency
8	F	4 plus	3 days	+	Acute cholecystitis, common duct obstruction	Cholecystectomy, common duct exploration	Leakage from cystic duct, subphrenic abscess, pancreatic necrosis
9	F	'	3 days	0	Acute cholecystitis, carcinoma of cecum	Cholecystectomy, ileocolostomy	Intestinal obstruction, hypertensive cardiac disease

\* No autopsy

that all but one were women and the duration of known biliary tract disease was of long standing—longer, I feel than the histories recorded. Furthermore, the duration of the immediate attack was of two days or more with one exception. Jaundice was marked in five of the patients.

In patients fifty years of age and over acute cholecystitis is a more serious disease than in the younger age group. The mortality rate is almost five times as great in this series. It has been our experience that changes in the vascular system, i.e., arteriosclerosis, hypertension and diabetes, are greater in those who have biliary tract disease than in a corresponding number without it. Cowdry in a volume on arteriosclerosis places the incidence of arteriosclerosis in the general population at 25.6 per cent for those between fifty and sixty, and 38 per cent for those over sixty. McCallum found that patients over fifty dying as a result of biliary tract disease associated with gall stones showed an incidence of arteriosclerosis of 68 per cent. The trend of our population toward the older age groups indicates that we may anticipate an increasing number of these geriatric problems unless they can be reduced by preventive surgery. For biliary tract disease it means operating in the earlier decades when acute cholecystitis represents an early phase of the disease. If our contention is correct, a deleterious effect upon the vascular system may be interrupted.

#### ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL

September 1, 1932, to September 1, 1945

##### *Patients Under Fifty Years of Age*

Total	352
Deaths	4
Mortality	1.13%

##### *Operative Procedures*

Cholecystectomy	320
Cholecystostomy	32
	(9% of total operations)
Common Duct Exploration	25

The remaining 352 of the 527 patients were under fifty years of age. There were four deaths, a mortality rate of 1.13 per cent, 320 or 90 per cent, were subjected to cholecystectomy, and 32, or 9.1 per cent, were treated by cholecystostomy. Only twenty-five or 7.1 per cent, had in addition to one of the above procedures exploration of the common duct. This is a far more favorable outcome than our experience with the group of patients who were fifty years and over.

SUMMARY OF DEATHS AFTER OPERATION  
UNDER 50 YEARS

Sex	Age	History of Biliary Disease In Years	Duration of Attack	Icteric	Findings	Operation	Cause of Death	
1	M	41	5 years	1 day	+	Acute cholecystitis	Cholecystectomy	Cardiac and renal failure, liver death
2	F	19	15 years	3 days	+	Acute cholecystitis	Cholecystectomy	Subdiaphragmatic abscess, peritonitis
3	F	19	12 years	2 days	0	Acute cholecystitis, stones in common duct, acute pancreatitis	Cholecystectomy, choledochotomy	Pulmonary emboli 27th p o day*
4	M	41	4 years	10 days	0	Acute cholecystitis	Cholecystectomy	Hypertension, cardio-renal failure

\* No autopsy

The chart (page 290) of the four deaths is self-explanatory and emphasizes in each instance that the biliary disease was of long standing. This suggests that acute cholecystitis is but a phase of the disease.

Given a patient with a definitely established diagnosis of acute cholecystitis, our policy provides for his or her surgical treatment as soon as adequate preoperative preparation has been carried out. There is no undue haste, no neglect of this preparation, and never is it to be undertaken where operation of any kind is contraindicated. It may require several hours to prepare these patients, no step should be neglected. A surgical operation on the biliary tract is to each patient a serious procedure, never to be entered into lightly, and those with acute cholecystitis are certainly no exception. Once prepared, the operation should be undertaken and the nature of that procedure and the extent determined by the findings and the general condition of the patient.

How different is this from the so-called conservative attack which considers these patients a medical problem, leaves them in their homes where complications may develop and be unrecognized. There can be little disagreement that in a well regulated hospital the constant observation and care of a patient will be far more efficient than in the home, where the patient may be seen once a day by the physician. I need not remind you that laboratory data, temperature records, and personal observation by more than one individual are of great value in determining the course of events in any pathological process.

It is the duty of the surgeons to present this to the general practitioner and to demonstrate that such a policy will diminish the deaths due to this particular entity if and when they are considered surgical subjects and are admitted to the hospital.

I feel that in the heat of argument there have been radical claims made by those who favor early operation and those who are opposed to it. Those in favor often insist that operation be done within a period of hours without dwelling long on preoperative preparation, and this certainly is not sound. On the other hand, those opposed to operation assume the policy that surgery is not indicated and that it should not be carried out, and they cite figures based not upon the early surgical treatment of acute cholecystitis but upon the treatment of the complications that arise from these cases.

In conclusion, it should be reiterated that successful surgery is dependent upon every detail associated with it, and the patient with acute cholecystitis is no exception. Pre- and postoperative care and meticulous surgery are necessary to support the policy that we maintain.



# TREATMENT OF CHRONIC CHOLECYSTITIS, WITH AND WITHOUT STONE INDICATIONS AND CONTRA- INDICATIONS FOR CHOLEDOCHOSTOMY\*

FREDERIC W. BANCROFT

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Two subjects have been assigned to me namely, chronic cholecystitis and indications and contraindications for choledochostomy

In the limited time assigned to me, it would be foolish for me to attempt to cover the problem of cholecystitis with stones This, I believe, is not the problem that bothers the clinical surgeon the most The clinical surgeon is perturbed by a patient who comes complaining of right upper quadrant pain, moderate flatulence, some tenderness over the gall-bladder and a cholecystogram that does not show presence of calculi The cholecystogram may or may not show a non-functioning gall-bladder

At the time of operation, a gall-bladder may be found with moderate thickening of the wall and the presence of some adhesions about the ampulla or fundus, or no adhesions There may be areas of subperitoneal fat deposits as described by Deaver and Willy Meyer No stones can be palpated in the gall-bladder This pathological condition has been aptly described by Evarts Graham as minimum cholecystitis It is this particular phase of gall-bladder surgery upon which I wish to concentrate Evarts Graham has described 4 types of chronic cholecystitis without stone These are, namely, and I quote him

"The term minimal lesion was assigned to those cases in which the gall-bladder wall was not greatly thickened, the organ contained concentrated bile and on microscopic examination there were a few lymphocytes in the wall

"A diagnosis of cholesterosis was made when the mucosa of the gall-bladder contained the yellowish plaques that are characteristic of lipid deposits

\* Presented February 1 1946 before the Section of Surgery, The New York Academy of Medicine in the Symposium on Surgery of the Gallbladder

"Chronic catarrhal cholecystitis was said to be present when there was edema of the mucosa, a greater infiltration of lymphocytes than in the minimal lesion and some muscular thickening

"Chronic fibrous cholecystitis was the term applied to those gall-bladders with markedly thickened walls, cuboidal epithelium that often is absent in places, and diverticular crypts. This type of lesion is almost always accompanied by biliary calculi."

The etiology of chronic cholecystitis without stones is still a disputed problem. There are four main possible etiological causes, no one of which describes all of the pathological findings of chronic cholecystitis. These are, namely

- 1 *Infection* The infection theory arises from the fact that infection may be carried to the gall-bladder through the common duct or through the lymphatics

Sappey has shown that "a considerably large number of fairly large lymph vessels pass along the inferior surface of the liver over the body of the gall-bladder from the adjoining quadrate lobe and the right lobe, to form an extensive anastomosing network of vessels in the neighborhood of the neck of the gall-bladder. Others, derived from the same sources, pass behind the gall-bladder to terminate in the same region. There are apparently numerous anastomosing lymph capillaries between the lymphatics of the liver and the gall-bladder."

Sudler and Evarts Graham have offered the hypothesis of the hemato-lymphatic route. Bacteria injected into the portal vein have been shown to form focal areas of infection in the liver and bacteria have been found in lymphatics surrounding the gall-bladder.

In 1924 I injected lamp black into the portal vein and found it on microscopic examination 48 hours later in the lymphatics surrounding the gall-bladder.

There are four possible concepts of infection of the gall-bladder.

- 1 Descending infection of the liver by bacteria carried down in the bile and ascending into the cystic ducts
- 2 Ascending infection from the duodenum up the common bile duct and thence into the lumen of the gall-bladder
- 3 Hematogenous infection of the gall-bladder and its bile ducts and
- 4 A spreading infection to the wall of the gall-bladder through the lymphatics arising in the liver

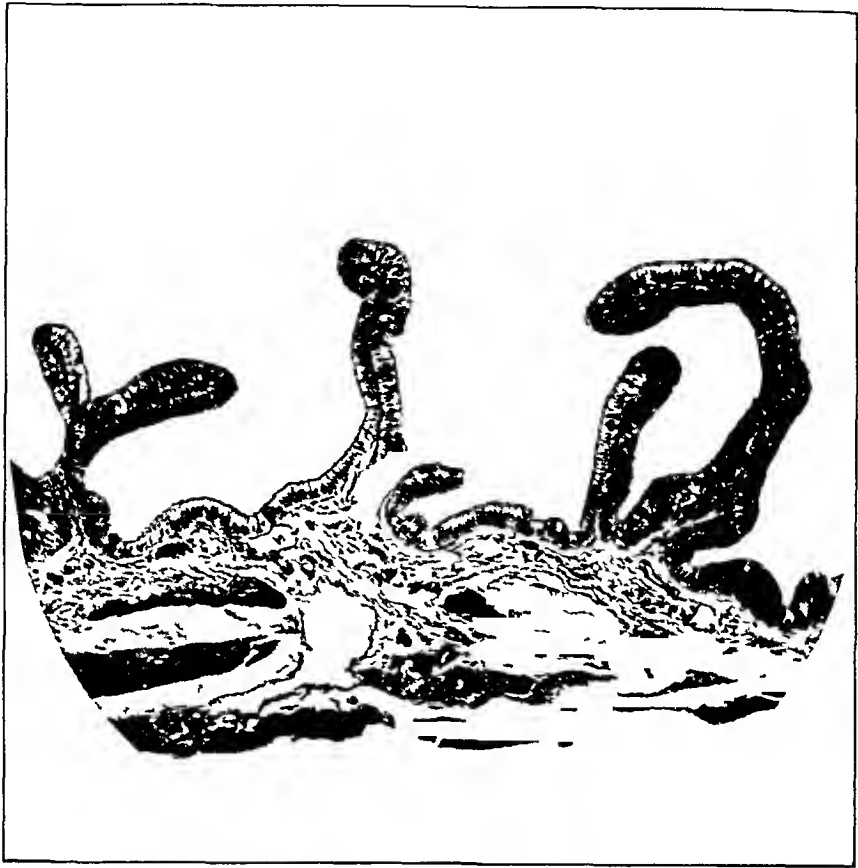


Fig 1—Normal gall-bladder removed at autopsy of traumatic case shortly after death. Thin stroma narrow elongated villi, no round cells in muscularis

It has been noted by many surgeons that chronic cholecystitis is often a sequel of suppurative lesions in the lower abdomen. In 1924, I published an analysis of thirty-eight consecutive cases of minimum cholecystitis without stone. In this particular series, eleven women and five men had had previous operations for inflammatory lesions of the lower abdominal organs. In opposition to the infectious theory is the fact that bacterial studies of the bile removed in most cases proved the bile to be sterile even in acute cholecystitis. Judd and his associates found a positive culture in the bile in only 14 per cent of the cases of cholecystitis and positive culture in the gall-bladder wall in 49 per cent.

2 *Cholesterosis of the gall-bladder, the so-called "strawberry gall-bladder"* This is a definite pathological entity which is grossly shown on observing the mucosa of the gall-bladder. It is non-infectious in

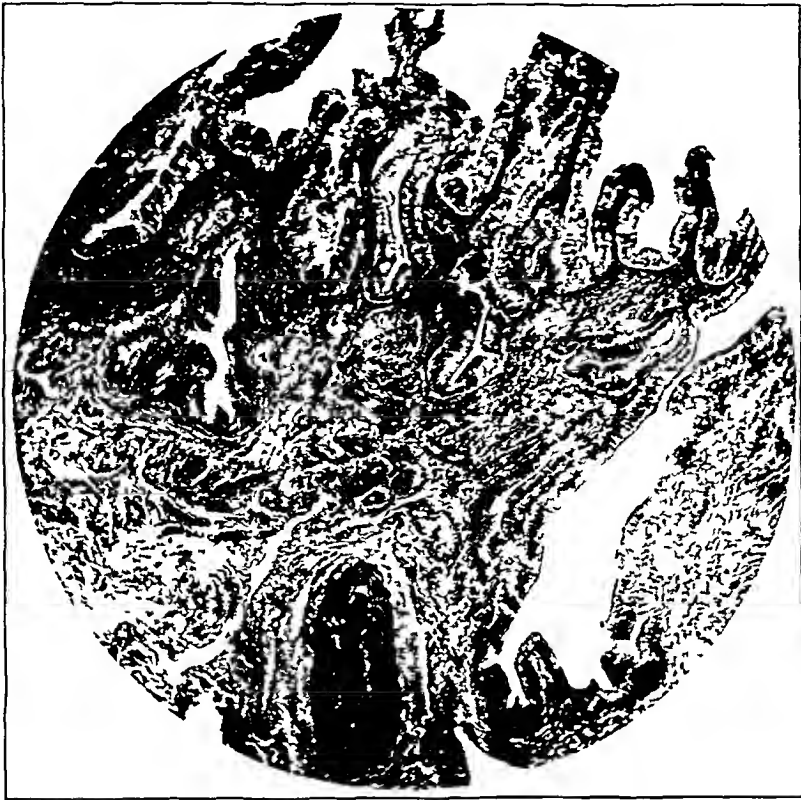


Fig 2—Chronic cholecystitis, seven years duration Gall-bladder adherent to duodenum Contained black bile on aspiration Granular fat seen on cystic duct Numerous round cells in muscularis and submucosa Cholecystectomy Patient well

character as far as I know, and is due to a chemical change in the bile. Cholesterol is deposited in the tips of the papillae causing thickening of the papillae and often associated with a round cell infiltration of the submucosa. Experimental studies show that even with this cholesterosis, the concentration of the bile by absorption through the gall-bladder wall is not greatly delayed.

3 *Reflux pancreatic ferments through the cystic duct into the gall-bladder.* Colp and Doubilet have shown that if there is an anomaly of the common duct so that the pancreatic duct enters into the common duct before it reaches the papilla of Vater in cases of spasm of the sphincter of Oddi, there may be a reflux passage of pancreatic juice associated with bile into the gall-bladder. Wolfer showed in experi-



Fig 3—Duration five years. Edema of villi. Thickening of muscularis with round cell infiltration. Cholecystectomy. Poor result.

ments with animals that where the pancreatic duct enters the common duct some distance proximal to the sphincter of Oddi, if he created a partial obstruction of the common duct between the entrance of the pancreatic duct and the sphincter of Oddi, a type of chronic cholecystitis with ulceration of the mucosa results due to pancreatic reflux.

4 *Partial obstruction of the cystic duct* Warren Cole has demonstrated that if a partial stricture of the cystic duct be created experimentally in animals, there is a concentration of bile double its normal content in the gall-bladder. He has been able to show that a type of chronic cholecystitis results.

We may readily assume from the summary of these various causes that we are not in common accord as to the pathology or etiology of chronic cholecystitis without stones.

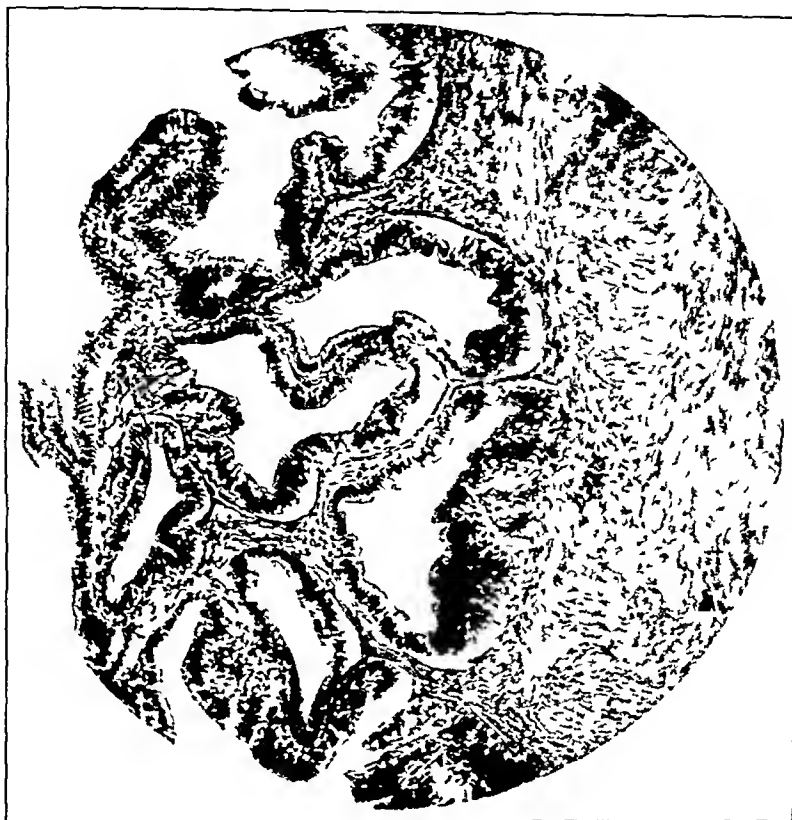


Fig 4—Duration four months, strawberry gall-bladder. Moderate round cell infiltration. Some thickening of villi. Lipoid deposit shown with special stain. Cholecystectomy. Good result.

In 1924, I summarized the histories, physicals, operative findings, microscopic and pathological findings and the follow-ups on thirty-eight consecutive operative cases on Dr. Pool's service at the New York Hospital. I was perturbed then, as I am now, in diagnosing and operating upon cases of minimal cholecystitis without stone. At that time we had most of the diagnostic measures that we have now, with the exception of the cholecystogram, and I am not at all convinced that the cholecystogram has added much to our diagnostic acumen, even in cases of non-filling of the gall-bladder. Evarts Graham, in a diagnosis of similar cases, felt that it was of no diagnostic significance in this type of case.

*Incidence.* There were twenty-four women or 63.2 per cent, with an average age of thirty-six at the time of operation, fourteen men,

TABLE I—IMPORTANCE OF PATHOLOGIC CHANGES TO PROGNOSIS AFTER CHOLECYSTECTOMY\*

	Well	Im- proved	Unim- proved	Postopera- tive Deaths	Total
Minimal lesion	11	22	21	3	57
Cholesterosis	14	2	14	1	31
Chronic catarrhal cholecystitis	18	16	13	4	51
Chronic fibrous cholecystitis	2	3	0	0	5
Cholesterosis with stone	6	11	0	0	17
	51, or 31.7%	54, or 33.5%			161

or 36.8 per cent with a similar average age at the time of operation. The average duration of symptoms analyzed was 2½ years.

*History Analysis* The chief complaint in this series was pain and soreness in the epigastrium or right upper quadrant. The pain radiated to the back in twenty-four, or 63.2 per cent of the cases. In nine of the cases it was described as dull and in twenty-nine as knife-like. Thirteen complained of indigestion and gas after eating, symptoms which had persisted over a considerable period of time. There was vomiting during the attacks in nineteen cases, or 50 per cent. Eleven women and five men had had previous operations for inflammatory conditions of the lower abdominal organs. In addition, five women and seven men had definitely diseased appendices removed at operation. This made the total number of patients with inflammatory conditions of the lower abdomen, twenty-nine, or 73.7 per cent.

*Physical Examination* Physical examination usually revealed patients with a moderate amount of adiposity. Usually they did not appear particularly ill. Rigidity was shown in a moderate degree in nine cases, marked in four, and absent in twenty-five. Tenderness in the right upper quadrant at Murphy's point on deep pressure was noted in thirty-five cases and absent in three. The ante-operative diagnosis was cholelithiasis thirteen times, cholecystitis fifteen times, adhesions about the duodenum four times, and ulcer of the duodenum two times. In four the ante-operative diagnosis was not mentioned.

*Operative Procedure* Cholecystectomy was performed thirty-one times, cholecystostomy was performed six times, and inversion of a

TABLE II—CHOLECYSTOGRAM AND PROGNOSIS 114 CASES\*

Type of Cholecystographic Response	Total	Clinical Results				Percentage Well or Improved
		Well	Im- proved	Unim- proved	Postopera- tive Deaths	
Normal gallbladder	10	5	1	4	0	60
Deformed shadow	8	4	2	2	0	75
Faint shadow	75	22	22	28	3	59
No shadow	21	6	7	5	3	62
	114	37	32	39	6	60

\* Note Tables I and II were found in A Consideration of the Stoneless Gallbladder by Evans, Graham M D, and W. Arthur Mackey, *JAMA* Nov. 17, 1934.

distal portion of the gall-bladder in hour-glass constriction, once

The appendix was removed in twenty cases and was found to be definitely diseased in twelve of the twenty as noted by the operator. Only definitely marked lesions of the appendix have been classed in this series as diseased.

*Follow-Up* Thirty-seven of the thirty-eight cases were examined and personally seen in the Follow-Up Clinic, for periods varying from six to thirty-nine months. There was no operative death in this series. There were three subsequent operations; one a case which came back for incision and drainage of an abdominal wound abscess three weeks after leaving the hospital. One case developed incisional hernia, and at a subsequent operation this was repaired. One case, cholecystostomy, came back complaining of pain. An operation was done, but the adhesions were so dense that no satisfactory operative procedure could be carried out.

Thirty cases were classified as good, and seven classed as poor, making a total of 81.5 per cent good results. Subdividing the series into operations, there were thirty-one cholecystectomies with twenty-seven good results and four poor results, or a percentage of 88.5 good results. There were six cholecystostomies with three good results and three poor results, making a total of 50 per cent with good results.

The case was classed as poor when abdominal pain and indigestion of varying degree still persisted. Five patients complained of indigestion and gas after eating. Eight patients complained of some upper abdominal pain. No history of vomiting was obtained in any of the post-



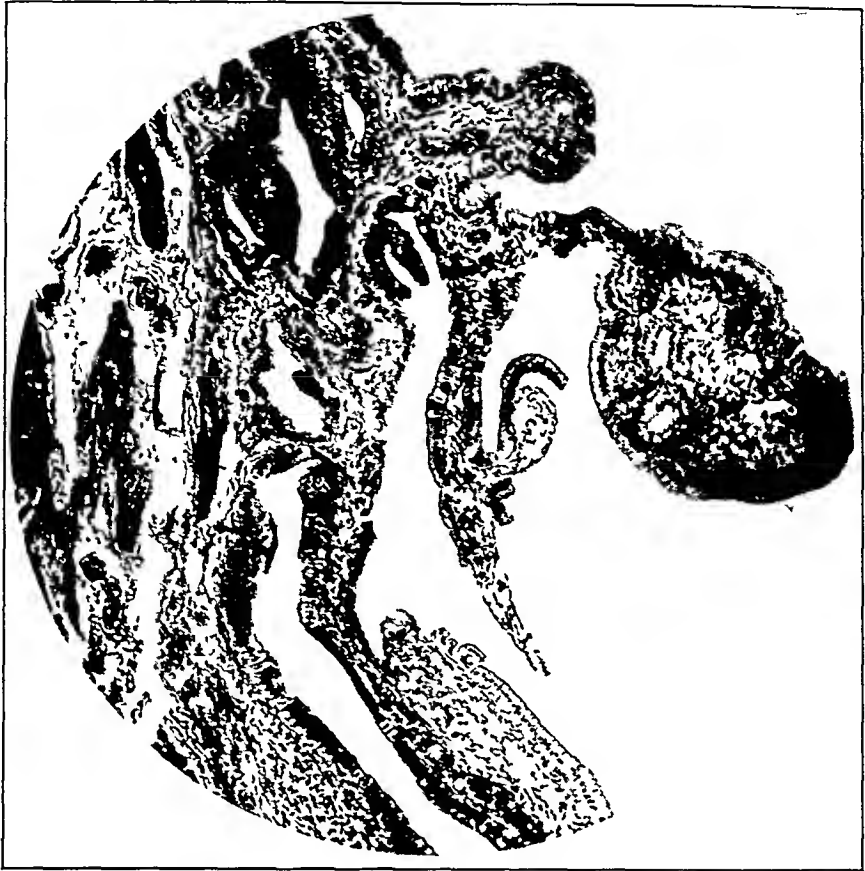


Fig 5—Eight years duration Gall-bladder found thickened at operation No adhesions Mucous membrane appeared slightly reddened Knob-like villi with some ulceration of mucous membrane Round cell infiltration Cholecystectomy Good results

operative cases Eight patients still complained of constipation

Graham has noted, as have others, that it is difficult to obtain a microscopic study of a normal gall-bladder as a comparison Also there must be involuntary changes throughout the years that create certain moderate changes in the gall-bladder that correspond with similar changes in the appendix The difficulty in obtaining a normal gall-bladder specimen for microscopic examination comes from the fact that these must be obtained from autopsies An autopsy is not usually performed immediately after death and autolysis takes place within the gall-bladder Douglas Symmers was good enough to obtain for me the gall-bladder of a young man who had been killed in an accident The gall-bladder was opened and imbedded in formalin within two hours



Fig 6—Strawberry gall-bladder, one year duration Thickened knob-like villi with edema and ulceration of the tips Cholecystectomy Good result

after the patient had been killed This specimen is the only normal gall-bladder that I have been able to find in the literature and I wish to show it with some of the photomicrographs of pathological specimens

There seem to me to be three different types of inflammatory lesions noted in the gall-bladder

- 1 Cholesterosis of the gall-bladder with thickened tips of papillae and deposits of cholesterol through the mucosa
- 2 Bulbous, edematous papillae, often with ulcerations of the mucosa and round cell infiltration of the submucosa
- 3 Thickening of the subserosal layers of the gall-bladder with dilated lymphatics often containing groups of polynuclear leukocytes with a round cell infiltration in the muscularis



Fig 7—Duration, one and one-half years Stain for lipoid deposit shows knob-like villi with lipoid deposit in mucosa and submucosa Cholecystectomy Good result

This latter group I assume to be due to extension of infection from the liver through the lymphatics anastomosing over the gall-bladder

I must confess that our result of 88.5 per cent good results is either due to the fact that we were very conservative on the cases operated on, as the average duration of symptoms was over 2½ years, or our series was too small. Four to five successive bad results would markedly change these figures, which are much better than the general results published. For instance, Evarts Graham states as follows

"The ultimate results in those cases in which no stones were present showed only 60 per cent of the patients considered themselves well. There was an equal number of gall-bladders which had a few adhesions as had many adhesions. In the class listed as greatly improved, nearly three times as many patients showed only a few adhesions

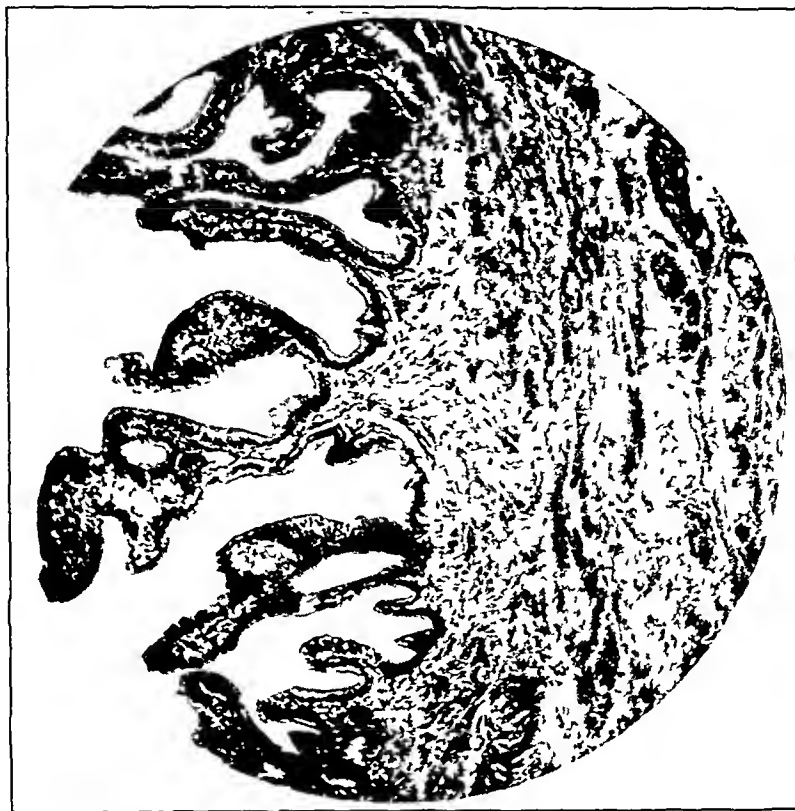


Fig 8—Numerous round cells seen in submucosa and muscularis Cholecystectomy Good result

around the gall-bladder. On the other hand, all of the seventeen patients with cholesterosis and stone showed either marked improvement or complete recovery from the symptoms.

"Of the stoneless cases only 33 per cent gave a history of biliary colic but 76 per cent of these patients consider themselves well or improved. On the other hand, only 58 per cent of those without biliary colic were well or improved."

#### SUMMARY

We must be extremely cautious in operating on patients when there is no evidence of biliary calculi. The Meltzer-Lyon test may aid us if we receive no help from cholecystograms. The B bile containing bile-stained bacteria or leukocytes is suggestive of a chronic cholecystitis.

TABLE III—MINIMUM CHOLECYSTOMY WITHOUT STONE

	<i>Good</i>	<i>Poor</i>		<i>Percentage of Cures</i>
31 Cholecystectomies	27	4	=	88.5
6 Cholecystostomies	3	3	=	50

It is unfortunate that one cannot open the wall of the gall-bladder, inspect its mucosa and then re-suture it. This procedure has proved disastrous in some hands. It is my opinion that if the patient has had right upper quadrant symptoms of pain with colic not as severe as colic due to calculus, which is persistent for at least two years, and if there is definite localized tenderness, we are justified in exploring. If the gall-bladder shows moderate thickening of the wall and poor emptying by compression, cholecystectomy is justified, although we must admit at that time that we will have a certain percentage of failures as far as curing the patient is concerned.

*Indications and Counter Indications for Common Duct Drainage History* If the patient has had a definite history of antecedent jaundice, the operator must convince himself that there is no obstruction in the common duct. Repeated attacks of severe vomiting with pain in the right lower dorsal region of the back is also suggestive of calculi in the duct. When the patient is operated upon, one must of course palpate the common duct. This method however offers numerous failures, as often surgeons have not felt any stone in the duct and on opening the duct have found calculi.

The gall-bladder containing numerous small stones, a thickened head of the pancreas, or a dilated common duct, is an object of suspicion. It is my impression however that we have gone too far to the left in our exploration of the common duct. For instance, Arthur Allen states that in his own personal series of 266 biliary tract operations, 159 cases, or 59.7 per cent of the total series had duct explorations, in whom stones were found in ninety-eight instances, i.e., 61.6 per cent of ducts explored revealed calculi, or a negative finding in 38.4 per cent, who were explored without finding calculi.

Frank Lahey, in discussing Allen's paper, stated that stones can be found in 18 to 20 per cent. In 4 per cent of Lahey's cases stones were not present in the gall-bladder and were present in the common

duct In 39 per cent of Lahey's cases where calculi were found in the common duct, jaundice was not present and never had been present

In analyzing my own cases, I find that I have explored the common duct and found calculi in 17 per cent of cholecystectomies and I have not found calculi in 10 per cent

I find, however, that my fear of leaving calculi is making me explore more ducts than I think should be explored The difficult problem I have encountered is whether or not a common duct is dilated and if it is dilated, is it due to the occlusion of the cystic duct with compensatory dilation of the common duct, or is it due to distal obstruction? There is no question that one increases the morbidity and mortality by unnecessary common duct drainage and I am coming to the conclusion that if the common bile duct, although dilated, does not appear thickened or inflamed, one is relatively safe unless there are other definite indications for incising the duct

Barney Brooks states that he never puts a tube in the common duct, that he closes it and drains to Morrison's space So far, I have not had the courage to follow this procedure but I believe that it may have definite merit It certainly saves the trauma of pulling any tube out of the duct when one wishes to discontinue common duct drainage

Aspiration of the common duct by needle puncture is an aid in determining if there be stones in the duct Clear bile without flakes of fibrin in it is a fairly good indication that no stone is present However a word of caution should be offered about needle aspiration Even with a fine needle inserted into the duct, bile is apt to leak from the puncture hole for a considerable period of time and drainage of Morrison's space must be established in cases where this has been done if the duct is not opened If the duct is opened immediately, cholangiograms taken on the operative table are a safeguard to assure the complete removal of calculi If an operating room is properly equipped, it should not lengthen the operative time to any great degree and may save the patient a secondary operative procedure

#### CONCLUSIONS

The tragedy of inflammatory common duct lesions from cholecystectomy will be adequately described by Dr Colp but I feel that we must stress the importance of a primary atraumatic cholecystectomy, and insofar as possible, a protection of the common duct in our operative procedure I have found no method of common duct drainage that seems to me harmless if a large series is analyzed

THE REPAIR OF STRICTURES OF THE  
COMMON AND HEPATIC BILE DUCTS\*†

RALPH COLP

Surgeon, The Mount Sinai Hospital

THE most frequent cause of benign stricture of the hepatic and common bile ducts is the ultimate result of a direct injury to these important structures during the course of a cholecystectomy. Inadequate exposure, hemorrhage and anatomic abnormalities may result in the inadvertent ligation, clamping, or excision of part of the hepatic or choledochus during the removal of the gallbladder. The accident is not often recognized at the primary operation and only the subsequent course of events and operative findings may reveal the traumatic nature of the pathology. But operative injury alone cannot account for the complete absence of most of the common bile duct in some patients. Whipple<sup>1</sup> discussed three instances of irreparable stricture of the choledochus in which he felt sure that the common bile duct had not been injured at the time of cholecystectomy. When these patients had become deeply jaundiced, requiring a second operation, nothing was found but a shred of dense connective tissue extending from the duodenum to the portal fissure. He felt that such an extensive destruction of the common bile duct could only be due to the necrotizing effect of an activated pancreatic reflux. It is barely possible that the cases of chronic choledochitis described by the French surgeons in which the common bile duct resembles a pipe stem and into which a fine probe could not be introduced may be caused by repeated pancreatic reflux rather than by biliary stagnation and subsequent cholangitis. There are other cases in which merely the terminal portion of the common bile duct is strictured, the narrowing being due either to a chronic pancreatitis or to a stenosis of the papilla of Vater secondary to local ulceration.

Secondary operations upon the extra-hepatic bile ducts in general and plastic procedures in particular, are often complicated and involved problems. They may be very time consuming and productive of shock

\* From the Surgical Service of The Mount Sinai Hospital, New York, N. Y.

† Read before the Surgical Section, The New York Academy of Medicine, February 1, 1946

These patients require adequate and careful preoperative preparation. Surgical exploration is best performed under continuous spinal anesthesia which produces excellent muscular relaxation and renders adequate exposure. During operation a continuous infusion of 5 per cent glucose in normal saline is administered to which blood and plasma may be added. The operative findings in these cases follow a general pattern. The intra-abdominal adhesions are usually firm and dense, and at times the line of demarcation between adjacent viscera appears almost indiscernible, and only sharp knife dissection will delineate their boundaries. The liver, invariably enlarged and occasionally cirrhotic, and the omentum, are usually bound to the peritoneal surface of the anterior abdominal wall and the colon is firmly plastered to the site of the gall-bladder bed. When the colon has been separated from the liver, and after the duodenum has been similarly freed, the pathology in the gastrophatic omentum may be revealed. Occasionally the foramen of Winslow is obliterated so that the familiar anatomic landmarks are extremely difficult to identify. But if the stricture is near the termination of the common bile duct, the dilated choledochus is easily visible. If the scar is in the mid portion of the common duct, a partial narrowing may be seen with a definite enlargement of the proximal canal. However, in most of the cases, only dense scar tissue is found in the region of the hepaticus. This area, bearing in mind the close proximity of the portal vein and hepatic artery should be explored first with a fine hypodermic needle for the aspiration of bile or mucus in the syringe indicates the location of the duct. An incision is then made along the needle as a guide and the surrounding scar is carefully excised, usually exposing a shortened and dilated hepatic duct. In one of our cases the operation had to be discontinued at this point because the general condition of the patient became so precarious that further surgery was deemed inadvisable. The hepatic ducts were simply drained, leaving the restoration of biliary intestinal continuity for a later date. In patients suffering from prolonged biliary obstruction with severe hepatic damage, a two stage operation may be the procedure of choice. Attempts in most of these cases to isolate the distal portion of the common bile duct in the gastrophatic omentum are futile, for even if it were found, the defect between the choledochus and the hepaticus and the disparity in their lumens would make any type of hepaticocholedochal reconstruction impractical.



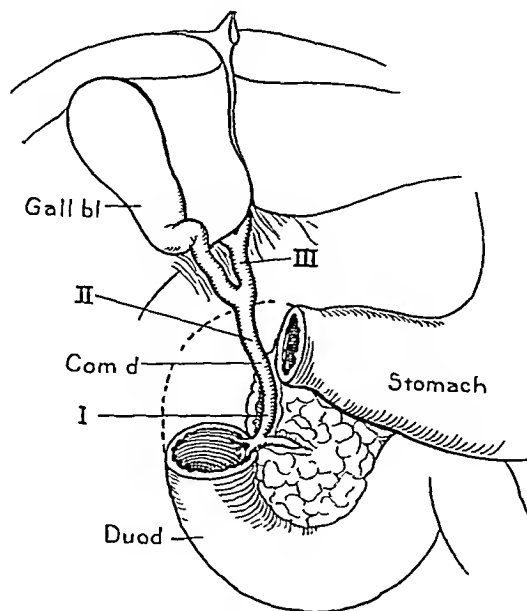


Fig 1—A diagnostic representation of the anatomy of the extrahepatic bile ducts

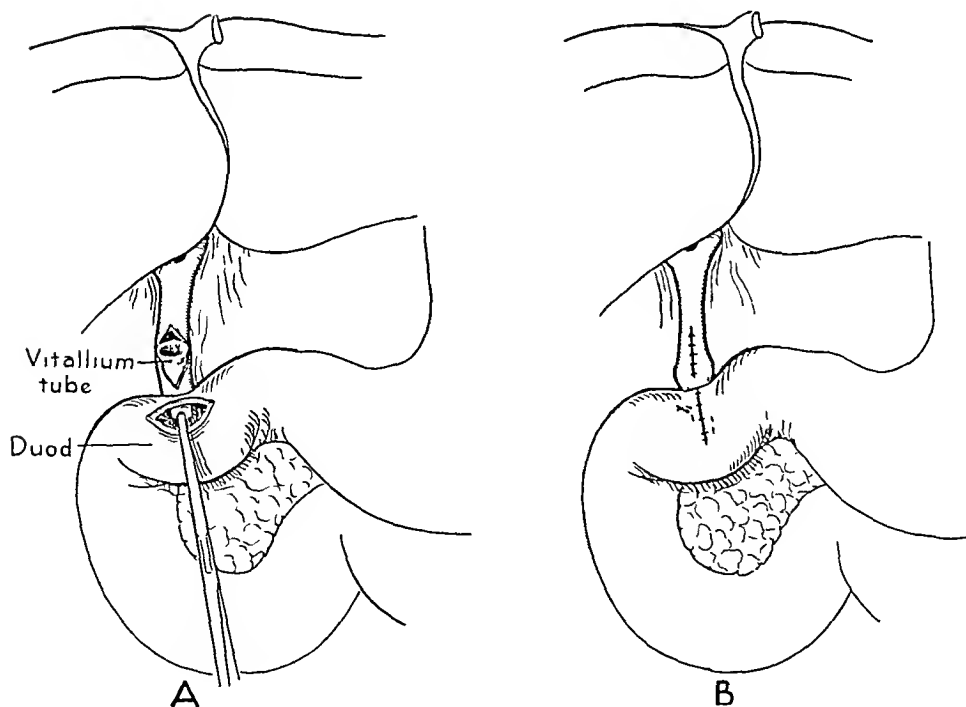


Fig 2 A & B—Choledochoduodenostomy. A method for the introduction of the vitalium tube for strictures of the papilla of Vater and terminal portion of the common bile duct

Once the location and the extent of the stricture has been established, a choice of operative procedure may be made, but there are certain cardinal principles which must be observed in any reconstruction of the bile ducts. It was Mayo who first emphasized the importance of uniting mucous membrane to mucous membrane in order to minimize the reformation of scar tissue and it is essential that any anastomosis between the divided duct or between the proximal duct and the intestine must be made without tension and with the maintenance of an adequate blood supply. And finally, if possible, the sphincter mechanism should not be by-passed.

The operative treatment of stricture may be arbitrarily divided into three groups (Fig. 1)

1 *The treatment of stricture of the papilla of Vater and the terminal portion of the common bile duct*

Occasionally the narrowed sphincter may be dilated by passing graduated sounds through the common bile duct into the duodenum followed if necessary by biliary duodenal intubation. A T or straight tube is inserted via the common bile duct and sphincter into the duodenum. This tube not only provides the delivery of bile into the intestine but its mechanical presence maintains a continual dilatation of the stenotic sphincter area until the T tube is either withdrawn or the straight tube is eventually passed by rectum. If the terminal portion of the duct is compressed by a chronic pancreatitis, the sphincter and the area of stricture may be by-passed by the suture anastomosis of the dilated common bile duct to the adjacent duodenum. Choledochoduodenostomy with or without intubation has been used frequently by many Continental surgeons. While many of the gastroduodenal roentgenograms in these patients demonstrated the presence of barium or air in the common bile duct and its radicles, the incidence of clinical cholangitis was not great. Recently in a case in which a choledochoduodenostomy with intubation was performed for a terminal duct stricture due to a marked pancreatitis, cholangitis occurred within four months, and reoperation disclosed no evidence of the previous anastomosis. The funnel shaped end of a vitallium tube was then introduced into the dilated common bile duct and its other end was drawn into the duodenum, the flange being sutured to the intestinal mucosa. The openings in the common bile duct and in the duodenum were then closed (Fig. 2A & B). The immediate result has been encouraging, but insufficient time has

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Fig. 3A & B—A case of chronic pancreatitis with stricture of the terminal common bile duct in which a choledochoduodenostomy was performed with the aid of a vitallium tube. X-rays show the tube in place and the regurgitation of air and biliary into the common bile duct and its branches.

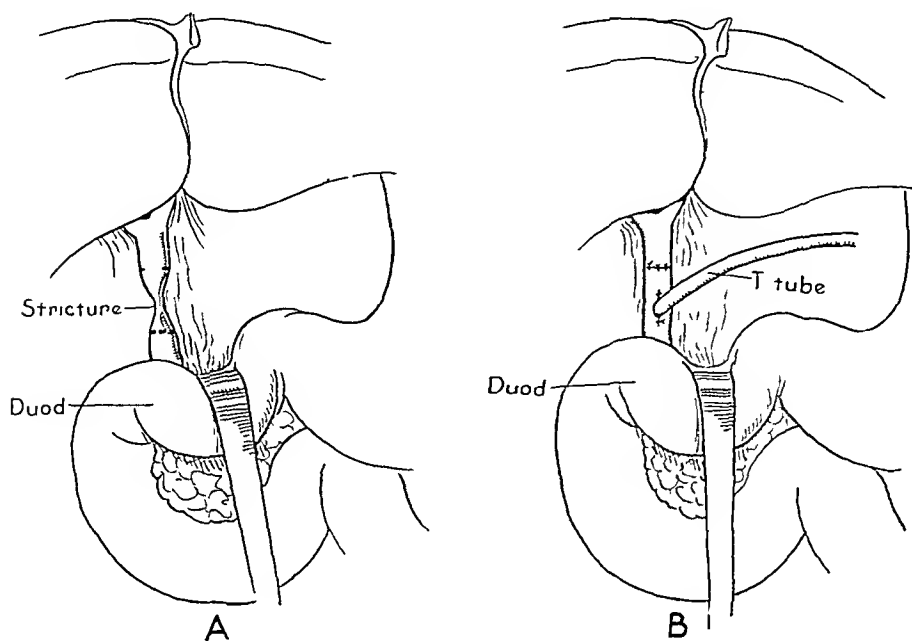


Fig 4A & B—A method of reconstruction of the strictured common duct, described by Cattell

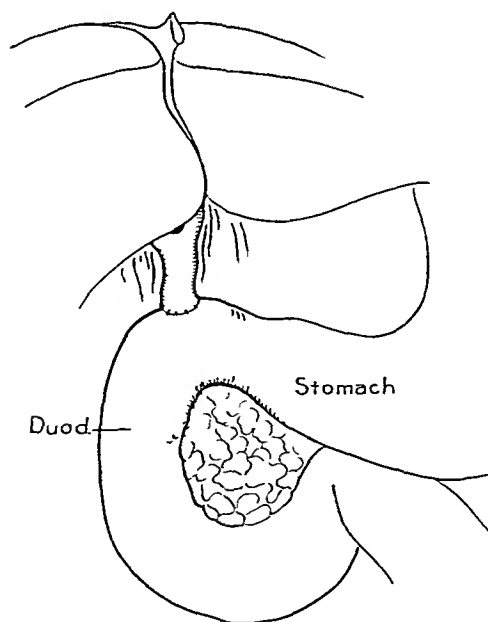


Fig 5—Hepaticoduodenostomy

elapsed to determine the eventual efficacy of this procedure, for while recent roentgenograms reveal the vitallium tube in place, the presence of air and barium in the bile ducts (Fig 3A & B) denote duodenal regurgitation

2 *The treatment of stricture of the mid portion of the choledochus*

In cases in which the extent of the stricture is limited, Cattell<sup>2</sup> recommends that the local area be resected with an end to end suture of the duct and the introduction of a T tube through a normal segment of the choledochus (Fig 4) The T tube is subsequently withdrawn Biliary duodenal intubation with either rubber or vitallium for large ductal defects covering the exposed tube with omentum is being used less and less A careful review of the literature reveals no incontrovertible evidence that this plastic procedure advocated by Sullivan<sup>3</sup> and McArthur<sup>4</sup> ever results in the actual regeneration of hepatic duct epithelium,<sup>5</sup> and while the sphincter mechanism is maintained, the gradual and eventual contraction of the fibrous connective tissue bridge between the reconstructed duct after the tube has been expelled may result in a secondary stricture with stasis and infection In this type of case, choledochoduodenostomy or choledochojejunostomy seems preferable

3 *The treatment of stricture of the hepatic duct*

In those cases in which an appreciable segment of the hepatic duct remains and the distal common duct appears obliterated, the dilated hepatic duct is freed of scar tissue and a direct suture anastomosis of the duct epithelium to the mucous membrane of the duodenum with or without intubation is done (Fig 5) This procedure requires the minimal amount of operative trauma, and the follow-up results in these cases are not too discouraging But in those instances in which there has been a complete destruction of the extra-hepatic bile ducts a permanent and adequate fistula must be established between the hepatic duct at the hilus and the intestine by the use of an indwelling tube reinforced by a suture of the serosa of the intestine to Glisson's capsule of the liver The material used for intubation may be either rubber, vitallium, or tantalum If rubber is selected, a fenestrated tube of highest quality, radio-opaque if possible and of sufficient tensile strength and calibre so that it will fit snugly into one of the hepatic ducts, is threaded on a heavy probe and introduced upwards into the liver This tube through its side holes usually drains both ducts effectively Its distal end, about 8 inches in length, is then passed into an opening made in

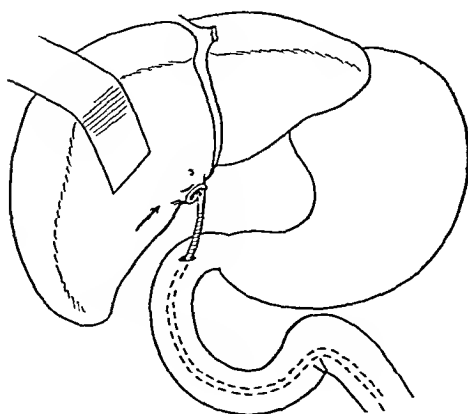


Fig 6A — Hepaticoduodenal Intubation. Fenestrated rubber tube inserted into left hepatic duct, and distal end directed through the duodenum toward the jejunum

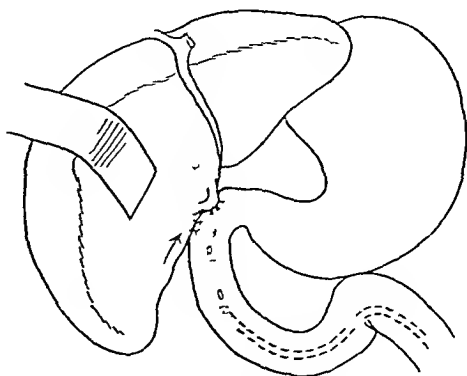


Fig 6B — Hepatoduodenostomy. Serosa of duodenum approximated to Glisson's capsule of the liver by interrupted silk sutures

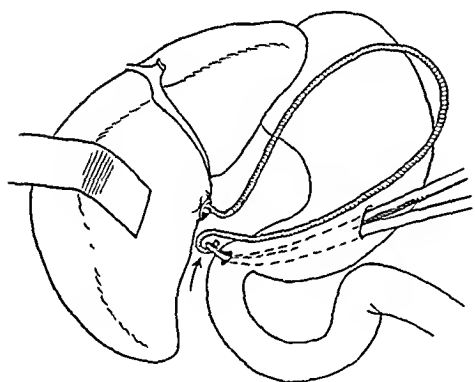


Fig 7A — Hepatico-duodeno-gastrostomy. Intrahepatic rubber tube pulled through a duodenotomy into the stomach by a clasp introduced through the pylorus

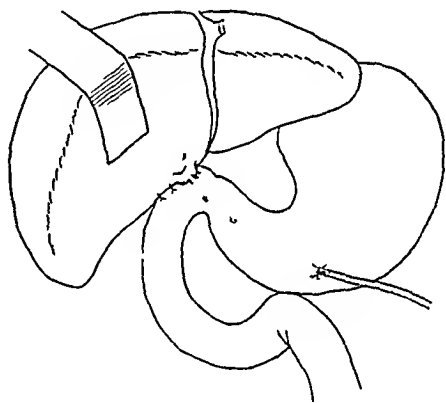


Fig 7B — Hepatoduodenostomy. Suture of the duodenum to the liver with interrupted sutures. End of tube made to emerge from stomach similar to a Kader Stamm gastrotomy

the opposing duodenal wall and directed preferably in the direction of the jejunum (Fig 6A & B). However, the tube may be pulled through the pylorus and brought out of the anterior wall of the stomach, similar to a gastrotomy (Fig 7A & B). Interrupted sutures of linen or silk then approximate the serosa of the duodenum to Glisson's capsule of the liver in the region of the intubation. Posterior and lateral sutures are tied before the anterior group is introduced. The area is then drained by rubber dams which emerge through a small right subcostal incision.

In the majority of our cases a complementary Kader Stamm jejunostomy for alimentation was performed, the enterostomy tube being drawn through a left lateral stab wound

The immediate postoperative complications in cases of anastomosis of hepatic duct to the duodenum, or the suture of the liver to the intestine with hepatico-intestinal intubation, may be due to leakage at the site of the anastomosis which may result in a biliary or intestinal fistula or a generalized peritonitis. Drainage has largely eliminated the latter as a complication. Occasionally there was a temporary seepage of bile which soon disappeared within a few days. In one of our cases, a debilitated female, 69 years of age, who had had three previous attempts at reconstructive procedures, the early and partial separation of the duodenum from the surface of the liver within 48 hours, resulted in a fatal peritonitis. In another case a dehiscence of the duodenal suture developed which terminated in a right subphrenic abscess and a massive empyema with multiple loculations. During the period in which the duodenal fistula was active, the intestinal secretions were aspirated by continuous suction and the chemical balances were regulated by the introduction of the aspirated contents, pabulum and electrolytes through the jejunostomy.

The use of the rubber tube in biliary duodenal intubation undoubtedly has some advantages and a few possible late disadvantages. The tube, because of its pliancy, is easy to handle and adapts itself to the mechanical conditions present. It relieves the obstructive jaundice. Its presence not only prevents an edema occluding the anastomotic site but in addition it acts as a supporting scaffold until the union between the duct and duodenum is firm. In the majority of reported cases, and in ours, the peristaltic activity of the intestine was sufficient ultimately to discharge the tube which was eventually passed by rectum in three to twelve weeks after operation. Some of the patients were unaware that the tube had been eliminated although x-ray examination failed to reveal its presence. On the other hand the tube may be retained indefinitely. It may be subsequently plugged with bile salts and then the resultant biliary stasis favors ascending infection. Judd<sup>6</sup> reported the retention of a tube for four years when a cholangitis developed which necessitated its removal two years later. However, innumerable occasions have been offered to examine tubes which have been retained for a year or more. Many of these are in a state of good preservation and

relatively free from encrustation and from the disintegrating effects of bile salts Andrus<sup>7</sup> cited a case in which the tube had been in place for eight years and still seemed to be serving its initial purpose It would seem desirable to be able to control the passage of the tube but older methods in which this was attempted were discarded because they were unsatisfactory In one of our cases in which the distal end of the biliary duodenal tube was brought through the pylorus and then out of the stomach, so that theoretically it could have been withdrawn at will, the early development of a gastric fistula necessitated its removal on the eleventh day The premature removal of the tube in this case at a time before a firm anastomosis had been established was probably the reason for an early recurrence of a secondary stricture and cholangitis

Pearse,<sup>8</sup> in order to eliminate some of the objectionable features of rubber, used vitallium tubes of various sizes and shapes especially designed to meet the particular mechanical conditions encountered in strictures of the extra-hepatic ducts He found that this metal did not corrode and bile salts did not precipitate on its walls Experimentally he noticed that the mucous membrane lining the tube failed to show any reaction although the mucous membrane did not grow into the metal tube But he added there was a general tendency for all tubes used in this work to eventually pass into the intestinal canal Undoubtedly a metal tube, with a flange at its center and funnel shaped at one end, introduced into the hepatic duct, may remain in place and maintain its patency for a longer period of time than a rubber tube However, recently Bettman and Tannenbaum<sup>9</sup> found it necessary to remove a 1 inch vitallium tube which they had implanted in a strictured common bile duct because the lumen was entirely plugged with a greenish deposit Moreover, a rigid vitallium tube in certain locations may be more difficult to handle than rubber, and the use of vitallium per se will probably not reduce the incidence of ascending infection from regurgitation, even though it maintains an adequate lumen between the liver and the intestine

In a group of seven patients in whom a hepatoduodenostomy with hepaticoduodenal intubation with a rubber tube was performed there was one death from a generalized peritonitis due to a duodenal leak Five of these patients have been previously reported in detail<sup>10</sup> There were four patients who after an immediate postoperative period have remained well and have never experienced any clinical evidence of an



ascending infection. One patient has been followed for five years, one for three years, one for two years, and one for five months. In the remaining two patients, persistence of a mild icterus has been noted and attacks of Charcot fever have been frequent, in one for the past four years and in the other for about two and a half years. At the onset the attacks were partially ameliorated by stimulating the intestine and the flow of bile by the use of saline cathartics and the infection was partially controlled by the careful administration of chemotherapeutic and antibiotic agents. In both these patients a recurrent stricture with chronic cholangitis is probably present. One patient was re-operated without success and the other has refused further surgery.

This serious complication of ascending infection due either to a recurrent stricture with biliary stasis or to intestinal regurgitation into the biliary radicles of the liver is always a possibility in any reconstructive procedure of the hepatic or common bile ducts, especially in those instances in which the sphincter mechanism has either been side tracked or eliminated. Over twenty-five years ago Eliot<sup>11</sup> stated that "the dangers of ascending cholangitis varies directly with the distance from the site of the papilla through which a new opening in the intestine was made. The result of subsequent regurgitation of intestinal contents is small if the end of the divided duct or the rubber tube in cases of reconstruction is passed obliquely (Witzel) through the intestinal wall. The risk of postoperative leakage, the subsequent formation of a duodenal fistula is also diminished by this procedure. For the purpose of still further decreasing these postoperative complications, provisions may be made for the insertion of the end of the divided duct, or in cases of reconstruction, of the rubber tube into a portion of the small intestine which has been excluded from the path of the intestinal contents by a simple entero-anastomosis or by a more complicated procedure," i.e., the Roux principle of intestinal anastomosis. At that time this procedure was rarely performed because the general condition of the patient did not permit a prolonged operation in view of the longstanding pre-existing jaundice. Today, however, the preoperative use of vitamin K, transfusions of blood and plasma, and the high protein and carbohydrate diet have practically eliminated the dangers of cholemia and have made these prolonged operations feasible.

In intractable cases of ascending infection following previous reconstructive procedures, it may become imperative to divert the flow

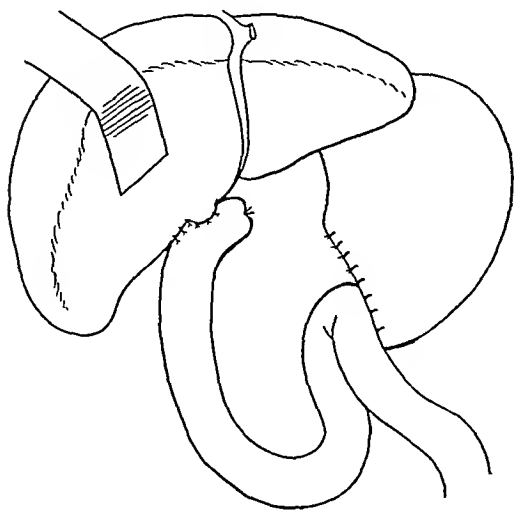


Fig 8—Subtotal gastrectomy of Billroth II type following hepaticoduodenostomy

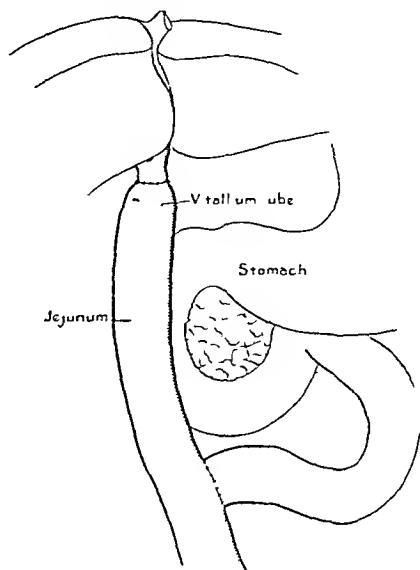


Fig 9—Hepaticojejunostomy over a vitallium tube with Roux Y type of intestinal anastomosis

of the intestinal contents and eliminate the factor of regurgitation. In cases in which a hepaticoduodenostomy has been done, Finsterer suggested that the gastric contents should be side tracked by a subtotal gastrectomy of the Billroth II type (Fig 8). This was done in one of our cases without any relief, but it is likely that this procedure was ineffectual because the infection had already become too firmly entrenched in the finer biliary ducts of the liver. The seriousness of ascending infection has been vividly re-emphasized in the past few years in those cases in which the enlarged gallbladder was anastomosed to the stomach following radical resections of the duodenum and the pancreatic head. In an effort to diminish the incidence of cholangitis and multiple liver abscesses which often terminated fatally, the severed dilated common duct was implanted into a loop of jejunum in which the food current was diverted either by an entero-enterostomy or preferably by a Roux Y type of intestinal anastomosis performed at some distance from the point of implantation. This latter procedure, advocated by Whipple,<sup>12</sup> Child,<sup>13</sup> and others, seems to have materially reduced the incidence of the Charcot syndrome. Recently, Cole, Ireneus, and Reynolds<sup>14</sup> have reported several cases in which the choledochus was almost

completely destroyed and in which a vitallium tube inserted in the hilar stump was anastomosed to the single arm of the jejunum utilizing the Roux principle. Then to further reduce the amount of intestinal regurgitation a series of intraluminal jejunal valves was constructed. This procedure has apparently eliminated attacks of cholangitis. The operation described by Coe was recently used in a case of biliary bronchial fistula secondary to a stricture of the hepatic duct. Unfortunately this patient developed a secondary hemorrhage on the second day from an arterial vessel injured at the time of operation, and she succumbed nine days after operation. There was no post mortem. The second patient, aged 22, was operated upon recently by P. Klingenstein<sup>15</sup>. She presented a stricture at the porta hepatis and following the implantation of a vitallium tube into the blind jejunal loop she made a good recovery and at present is convalescent. No further x-ray studies with barium have been made.

#### COMMENT

As the literature of reconstructive procedures for strictures of the common and hepatic bile ducts is reviewed, and one's personal experiences are studied, certain depressing facts become apparent. It is evident that the operation of cholecystectomy is not a simple innocuous procedure because the most frequent cause of benign stricture is the accidental injury of the ducts during the removal of the gallbladder. Stricture of the extra-hepatic ducts resulting in biliary obstruction and infection is an exceedingly serious condition. Various plastic procedures designed to restore biliary intestinal continuity are extremely difficult and are attended by an appreciable operative mortality. Furthermore, the follow-up studies of these patients reveal that many suffer from the effects of the local reformation of scar tissue and from ascending infection. Therefore, any reconstructive procedure which will maintain the calibre of the duct and the sphincter mechanism is greatly to be desired. Unfortunately the pathology in the majority of cases makes this impractical. In many cases it becomes necessary to anastomose the extra-hepatic duct or its hilar stump preferably to the duodenum or the jejunum over a tube. For intubation, rubber, vitallium, or tantalum may be used. Biliary intestinal intubation provides the immediate relief of the obstructive jaundice and should act as an intraluminal support until the anastomosis is firmly healed. The vitallium tube is favored at present

because it is retained longer, and is less apt to be clogged by the precipitation of bile salts but its presence per se does not diminish the incidence of either duodenal or jejunal regurgitation, a factor in the production of the Charcot syndrome. The reason why certain patients will develop attacks of ascending cholangitis in the presence of an adequate biliary intestinal fistula is not clear. The fact that some of these patients may be subsequently relieved of cholangitic episodes by secondary operative procedures in which the intestinal current is diverted and the degree of regurgitation reduced raises an important question. Should the operation of hepaticoduodenostomy or hepatoduodenostomy with hepaticoduodenal intubation be continued as a primary procedure, performing at a later date if necessary a subtotal gastrectomy of the Billroth II type to divert the gastric contents in cases of ascending infection or should these cases be treated initially by hepaticojejunostomy or hepatojejunostomy with intubation, utilizing the Roux principle of intestinal anastomosis with the hope that the primary diversion of the intestinal content will lessen the incidence of cholangitis? This is a fundamental problem which only the following results in these respective groups of surgical procedures will decide.

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## THE TREATMENT OF SEASONAL AND NON-SEASONAL HYPERESTHETIC RHINITIS WITH ANTHALLAN\*

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I<sup>N</sup> THE practice of rhinology, one of the most distressing symptom complexes, both to the patient and his physician, is the chronic hypersensitive nose. The characteristic symptoms of this condition are sneezing, watery nasal discharge, itching of the nose or eyes, and intermittent nasal obstruction. The physical signs are a change in the color of the mucous membrane, increased nasal secretion, and increased thickness of the mucosal lining. Microscopic examination of the secretion shows the absence of bacteria and the presence of excess numbers of eosinophiles, and roentgenograms and lavage of the sinuses show absence of infection. Infection of the nasal mucosa and the paranasal sinus mucosa can produce a similar symptom complex to that found in the hypersensitive nose, and it may exist concurrently in patients with a hypersensitive nose. However, all cases in which infection of the upper respiratory tract could be demonstrated were excluded from this study.

Williams<sup>1</sup> describes "chronic hypersensitive nose," named by him "intrinsic allergy," as "a fundamental, inherited, localized, cellular abnormality, resulting in some change in the cellular permeability and concomitant release of histamine when the deficient cell is affected by stimuli which obtain little or no response from the normal cell." Best and McHenry<sup>2</sup> state that the release of histamine into the tissue of animals produces arteriole constriction, capillary dilation, and subsequently, edema in the area as the permeability of the capillary walls increases. Many factors which elicit or influence this response have been studied clinically and experimentally, and evidence exists to show that one or more of the following influences also plays a part in cases of

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chronic hypersensitive nose specific allergens demonstrated by skin testing, endocrine dysfunction, psychopathic personality, physical agents such as heat, cold, and humidity, and local and systemic infection

The complicated nature of the problem presented by each individual having this symptom complex makes an accurate diagnosis difficult. Many physicians have no access to adequate laboratory facilities and x-ray apparatus. Moreover the average patient cannot afford the expense of adequate skin testing, a psychiatric study, or a series of special laboratory examinations. The unsatisfactory diagnostic aspect is paralleled by an unsatisfactory status of treatment. Many patients undergo a period of extensive testing in the search for specific allergens, followed by another period during which desensitization by means of specific allergic substances or nonspecific agents is used in an attempt to relieve the symptoms. This procedure is time consuming, and not always successful. Rhinologists of the conservative school have relied upon the local application of vasoconstrictors, the administration of sedatives, and the application of caustics to the nasal mucosa. The members of a more radical group cauterize the turbinate bodies, trim them surgically and straighten the septum in the attempt to create more air space in the nose. The most radical approach to the problem is to remove the turbinate bodies, excise the ethmoid sinuses, and remove the lining of the maxillary and sphenoid sinuses. In general, only temporary, partial relief is obtained by topical application or by surgical treatment.

Anthallan, 3'di(n-butyl)amino-methyl-1,4,5,6-trihydroxy-benzo(1,2,-c)furan-1'(3')-one, which is administered by mouth, makes possible an entirely different management of this type of case. Not only can hyperesthetic rhinitis be treated simply and effectively with this drug, but the diagnostic problem can be ignored. This report was prompted by the impressive results obtained in the treatment of 108 cases of seasonal and non-seasonal hyperesthetic rhinitis in private practice, and also by the success reported in the treatment of neurodermatitis disseminata and urticaria<sup>3</sup> with Anthallan.

According to one of the investigators, this drug showed its capacity to decrease the threshold sensitivity to histamine. However, this property alone does not explain sufficiently its action in the treatment of hyperesthetic rhinitis.

The toxicologic data submitted with this drug indicate that the drug has a low toxicity, e.g., the median lethal dose for the enterally

administered drug is over 30 gm per kilogram in the mouse, over 20 gm per kilogram in the dog, and over 10 gm per kilogram in cats, guinea pigs and rabbits. A high multiple of the therapeutic dose, given daily over periods of 1 to 2 years, was tolerated by rats, guinea pigs and mice with no changes demonstrable in microscopic pathology. In studies of blood and urine performed during and at the termination of these long-term feeding experiments with Anthallan at dosage levels up to 200 mg per kilogram daily, no significant differences in body-weight were found between controls and Anthallan-fed animals, with respect to blood cell count, blood formation, blood cell picture, blood sugar level, or kidney function.

It is well known that the severity of the symptoms of hyperesthetic rhinitis in a given individual varies from season to season, from day to day, and often from hour to hour, so that the cyclic fluctuation is often unpredictable. For this reason a careful selection of cases was believed to be of utmost importance in order to obtain conclusive information about the effectiveness of this drug. The patients studied were selected from those attending the Outpatient Department of the Otolaryngological Service of the Columbia University Presbyterian Hospital Medical Center. All patients so selected to whom a course of Anthallan treatment was given are included in this study. Criteria for selection follows:

1. Patients were selected who gave a history of persistent nasal obstruction and who showed the physical signs of increased nasal secretion, decreased breathing space, and a change in the color and appearance of the nasal mucosa. Patients in whom infection or mechanical obstruction of the nose could be found were eliminated after the first examination.

2. Patients who showed no gross evidence of upper respiratory infection, but whose nasal secretion contained an excessive number of bacteria or inflammatory cells were not accepted.

3. Patients in whom roentgen examination showed the presence of normal sinuses or sinuses with minimal thickening of the lining membrane were accepted, while those with a diagnosis of clinical sinusitis were not accepted.

4. Patients with an active systemic disease such as syphilis, nephritis, diabetes or infectious bronchitis were not considered acceptable.

Patients were selected whose symptoms had existed for a long period of time, the average being 506 days, prior to this study. No patient was

selected for study at a time of year during which he was usually free from symptoms or at a time when his condition in former years had had a tendency to improve. Although the cases selected satisfied the diagnostic criteria for hyperesthetic rhinitis, some individual differences were apparent. The following table shows that some patients were sensitive to specific allergens. It also shows the number of patients whose hyperesthetic rhinitis was seasonal, non-seasonal, and both.

It was difficult to select a name for the condition these patients had in common. The following names under which these cases have been listed in general usage were discarded: "Nonseasonal hayfever," "physical allergy," "allergic rhinitis," "nasal allergy," "intrinsic allergy," all imply the presence of an allergen, yet in many cases no allergen can be demonstrated. "Chronic Rhinitis" implies the presence of an inflammatory process, yet in many cases no infection can be shown. "Vasomotor Rhinitis" places the emphasis on the instability of the blood flow but disregards the lymphstasis. A name was desired which would permit the inclusion in this study of cases in which a specific allergen had been found. Seasonal and non-seasonal "*Hyperesthetic Rhinitis*," has been chosen as the most descriptive name because, first, it suggests the element of hypersensitivity of the nasal mucosa, secondly, perennial and seasonal cases may be included, and third, it implies the symptoms of excessive nasal discharge, excess sneezing, and nasal obstruction of which these patients complain.

Conditions were controlled as much as possible during the experiment. No patient was allowed to change any factors such as his surroundings, diet, or activities which might conceivably affect the severity of the nasal symptoms. Therefore, any remission of these symptoms during Anthallen therapy can be attributed only to the influence of this drug.

In order to make the evaluation of the subjective symptoms and the clinical findings as unbiased as possible, several observers examined each patient each week. They took into consideration only those phenomena which can be expected to respond to a drug, these "responsive features" are the patient's statement about his symptoms, the color of the mucous membrane, the amount of breathing space and the amount of visible secretion in the nose. The observer gave each of these essential symptoms a numerical value, using a scale of 5 grades 0 to 4 which was entered in a rating chart. In order to determine the percentage of



Table I  
ALLERGEN SENSITIVITY IN 42 PATIENTS WITH  
HYPERESTHETIC RHINITIS

	<i>Cases</i>	<i>Percentage</i>
Specific allergens found by skin testing	16	38%
No allergens found by skin testing	3	7%
Not tested	23	55%
Total	42	100%
Seasonal Hyperesthetic Rhinitis	4	9.3%
Nonseasonal Hyperesthetic Rhinitis*	31	76.2%
Seasonal and Nonseasonal Hyperesthetic Rhinitis	7	14.5%
Total	42	100%

\* One case of nonseasonal hyperesthetic rhinitis was limited to a portion of the menstrual cycle.

Table II—SUMMARY OF SIX PATIENTS WHO DID NOT COMPLETE  
THE COURSE OF ANTHALLAN THERAPY

<i>Case No</i>	<i>Cause for Stopping Treatment</i>	<i>Duration of Disease</i>	<i>Treatment Days</i>	<i>Improvement on Last Examination</i>
1	Acute bronchopneumonia	47 days	7	Exam 2 mo later 100% relief
2	Skipped one week	96 days	14	90% relief
3	Contradictory statements	"years"	21	75% relief
4	Refused to return to clinic	10 years		
5	Contradictory statements	240 days	7	50% relief
6	Bilateral purulent antral sinusitis	10 years		0

improvement after Anthallan treatment, a patient's average rating for a single day's examination was compared with his average rating before treatment. Since the numerical evaluation does not always express the whole clinical impression of the patient's condition, a short statement, called "medical estimate," was also made at the time of each examination.

Forty-eight patients were selected according to the diagnostic criteria, from a great number submitted by the resident staff, attending staff, and by personal application. Six of the patients who failed to complete the course of treatment in the manner prescribed had to be eliminated from the series as inconclusive. However, Table II shows that the response of these six patients who did not complete the course of Anthallan was comparable to the response of the conclusive cases.

Table 11A—INFLUENCE OF ANTHRALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthrallan Treatment Recorded on Numerical Rating Chart

<i>Case</i>	<i>Duration of disease y-years m-months</i>	<i>Age (years)</i>	<i>Duration of present attack (day)</i>	<i>Treatment (days)</i>	<i>Dosage (capsules)</i>
1	12 v	16	30	21	153
2	3 v	21	130	35	225
3	16½ m	13	496	13	60
4	6 v	31	60	21	126
5	4 v	18	1200	28	154
6	1 v	12	360	21	149
7	2 v	42	720*)	21	98
7a**)	—	—	—	14	112
8	6 v	13	1080	21	119
9	3 v	17	1080	21	133
10	3 v	34	1080	21	133
11	2 v	21	720	28	154
12	4 v	30	1440	7	35
13	4 m	28	120	14	77
14	6 m	42	180	21	175
15	5 m	37	150	21	92
16	5 v	27	1800	21	170
17	8 v	45	360	26	166
18	2 m	44	70	21	133
19	9 m	27	270	35	220
20	8 m	12	240	7	35
21	5 v	13	720	28	231
22	4½ m	40	135	21	151
23	8 v	10	210	21	133
24	3 v	37	1080	21	161
24a**)	—	—	—	21	154
25	20 v	39	390	21	168
26	4½ v	40	77	21	147
27	4 m	58	120	21	166
28	2½ v	39	540	21	85
29	20 v	42	360	14	77
30	1 v	39	11	21	136
31	2½ v	20	900	28	161
32	3 v	26	1080	21	133
33	6 v	40	R***)	21	133
34	3 m	30	90	21	133
35	25 v	40	R	21	133
36	8 m	28	240	28	203
37	18 m	25	540	14	84
38	5 m	37	150	21	133
39	26 v	57	R	21	146
40	5 v	35	R	28	190
41	2 v (42)	27 (42)	R (36)	16 (44)	108 (44)
42	R	44	R	16	130
<hr/>					
Total	200 2	1,296	18,229	925	6048
Average	43¼ v	31	506	21	137

\*) This case had symptoms for two years regularly at every menstrual period for 6 days 3 days before and after the onset of menstruation (see individual case report)

\*) Repeat course of Anthrallan

\*\*) R. Ragweed Hayfever

Table IIB—INFLUENCE OF ANTHALLAN UPON SEASONAL AND  
NONSEASONAL HYPERSENSITIVE RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

<i>End of Anthallan Treatment</i>			
<i>Case</i>	<i>Complaints</i>	<i>Physical Examination</i>	<i>Medical Estimate</i>
1	86	100	85
2	100	86	75
3	100	100	100
4	100	100	100
5	83	66	80
6	75	75	50
7	76	75	75
7a**)	90	77	100
8	100	100	100
9	78	100	100
10	78	90	90
11	83	82	80
12	100	100	100
13	100	100	100
14	0	0	0
15	83	100	100
16	71	67	75
17	69	50	50
18	38	83	75
19	86	75	75
20	96	100	100
21	75	75	75
22	28	30	40
23	86	100	100
24	89	88	90
24a**)	—	—	100
25	87	70	75
26	66	63	60
27	25	83	75
28	12	17	0
29	70	100	100
30	0	0	0
31	50	17	80
32	96	80	90
33	100	100	100
34	70	67	75
35	95	75	75
36	95	100	100
37	75	100	75
38	0	0	0
39	54	37	30
40	87	64	50
41	100 (43)	100 (43)	100 (44)
42	95	100	100
	3,149	3,022	3,310
	73	70	75

\*\* ) Repeat course of Anthallan

Table IIC—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

<i>Persistence of Therapeutic Result in Post-Treatment Period</i>			
<i>First Observation</i>			
<i>Case</i>	<i>Complaints</i>	<i>Physical Examination</i>	<i>Medical Estimate</i>
1	100	100	100
2	100	71	75
3	100	100	100
4	78	75	50
5	72	100	90
6	50	50	50
7	50	50	50
7a**)	100	100	100
8	90	94	75
9	67	83	40
10	—	—	—
11	83	82	80
12	100	100	100
13	—	—	—
14	0	0	0
15	83	83	75
16	71	—	75
17	33	25	25
18	87	100	75
19	86	75	90
20	96	100	100
21	58	69	75
22	40	40	40
23	100	100	100
24	89	88	85
24a**)	—	—	—
25	—	—	—
26	66	75	60
27	92	100	100
28	—	—	—
29	—	—	—
30	—	—	—
31	15	47	20
32	96	80	100
33	100	100	100
34	70	67	75
35	95	88	95
36	55	50	50
37	100	100	100
38	0	0	0
39	87	73	75
40	—	—	—
41	— (31)	—	— (34)
42	— [33]	— [33]	— [33]
	2,509		2,425
	[2,438]	[2,335]	[2,350]
	74		71
	[74]	[71]	[71]

\*\* ) Repeat course of Anthallan

\\\\\\ In [ ] parenthesis re examined cases only

In ( ) parenthesis number of cases in individual column

Table IID—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERTENSIVE RHINITIS

### Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

Persistence of Therapeutic Result in Post-Treatment Period				
Case	Complaints	Second Observation		Interval from End of Anthrax Treatment to Last Post-Observation Entry (days)
		Physical Examination	Medical Estimate	
1	86	100	100	54
2	61	71	75	40
3	100	100	100	248
4	—	—	—	27
5	—	—	—	7
6	43	50	50	34
7	—	—	—	14
7 <sup>a**</sup> )	70	77	75	89
8	90	94	75	118
9	—	—	—	34
10	—	—	—	—
11	100	100	100	78
12	—	—	—	14
13	—	—	—	7
14	0	0	0	—
15	83	92	90	141
16	—	—	—	20
17	—	—	—	14
18	100	100	95	86
19	86	75	75	56
20	100	100	100	55
21	96	100	90	34
22	40	40	40	35
23	100	100	100	105
24	84	76	75	103
24 <sup>a**</sup> )	—	—	—	—
25	—	—	—	****)
26	97	100	76	30
27	92	83	75	74
28	—	—	—	—
29	—	—	—	—
30	—	—	—	—
31	—	—	—	7
32	79	70	75	48
33	—	—	—	21
34	85	50	75	21
35	—	—	75	34
36	50	63	75	21
37	—	—	—	21
38	—	—	—	14
39	—	—	—	7
40	—	—	—	—
41	—	—	—	—
42	— [21]	— [21]	— [21]	— [35]
	1,640	1,641	1,616	1,711
	[78]	[78]	[77]	50

\*\* ) Repeat course of Anthallan

xxxx) In [ ] parenthesis 1e examined cases only

\*\*\* (patient went abroad at end of Anthyllan treatment)

TABLE III—SURVEY OF INCIDENCE OF ANTHRAZAN UPON 42 CASES (11 COURSES) OF 51 ANONAL AND NON-51 ANONAL HYPERTHYPIC RHINITIS

	number of Cases number of Anthrax Cases age (years)	percentage of all cases showing complete disappearance of symptoms*) (In parenthesis number of cases)	percentage of all cases showing fair improvement***) number of cases)	failure****)			number of cases in which improvement increased (with status at end of anthrax period)		Average per cent improvement cases in all
				minimum	maximum	average			
A result at end of anthrax treatment, as rated from	a "Complaints"	13	76(21)	16(7)	10(1)	—	—	73	
	b "Physical Examination"	13	33(11)	19(8)	10(1)	—	—	70	
	c "Medical Estimate"	11	11(18)	11(5)	9(1)	—	—	75	
B result at first re- examination in post- treatment period as rated from	a "Complaints"	31	11(15)	23(8)	9(3)	9	16	71	
	b "Physical Examination"	33	36(12)	23(8)	6(2)	8	11	71	
	c "Medical Estimate"	31	39(13)	21(7)	9(3)	9	17	71	
C result at second re- examination in post- treatment period as rated from	a "Complaints"	21	52(11)	19(1)	5(1)	5	7	76	
	b "Physical Examination"	21	35(5)	19(1)	5(1)	1	5	78	
	c "Medical Estimate"	21	62(13)	9(2)	5(1)	7	6	76	

a) 100% improvement	*)	25 to 60% improvement
b) 70 to 99% improvement	*)	less than 25%, improvement

Table IVA—LABORATORY STUDIES

Case	Sex	Blood Cell Count					
		Hb %		RBC		WBC	
		a	b	a	b	a	b
1	F	96	90	4,590,000	4,370,000	6,000	5,600
2	F	90	89	4,540,000	4,450,000	5,250	4,050
3	F	100	108	4,610,000	4,900,000	7,200	7,000
4	F	104	90	5,120,000	4,490,000	9,000	9,400
5	F	92	92	4,180,000	4,510,000	6,800	5,900
6	F	88	84	4,030,000	4,210,000	5,800	7,000
7	F	90	82	4,380,000	4,460,000	8,650	7,950
8	M	90	88	4,510,000	4,620,000	6,750	5,500
9	F	100	—	4,650,000	—	6,800	—
10	M	84	—	3,710,000	—	5,900	—
11	F	84	—	4,420,000	—	10,150	—
12	F	102	—	4,910,000	—	5,950	—
13	F	100	91	4,860,000	4,300,000	7,400	9,280
14	F	80	79	4,630,000	4,490,000	5,300	5,400
15	F	88	101	4,450,000	4,820,000	5,800	6,400
16	F	100	—	5,950,000	—	7,450	—
17	F						
18	M	96	87	4,720,000	4,520,000	6,100	7,810
19	F						
20	F	81	82	4,350,000	4,080,000	6,700	6,650
21	F	97	87	4,510,000	4,400,000	4,150	6,150
22	F						
23	M	101	80	4,890,000	3,940,000	9,900	6,450
24	M	96(22)	93	4,280,000(22)	4,800,000	5,750(22)	4,650
25	M	88[17]	86[17]	4,000,000[17]	4,000,000[17]	5,100[17]	4,600[17]
Total**)		2137		100,290,000		147,900	
		[1567]	1509	[76,650,000]	75,360,000	[111,650]	109,090
Average		97		4,559,000		6,720	
		[92]	[89]	[4,509,000]	[4,433,000]	[6,568]	[6,417]

a Test before Anthallan treatment.

b Test near end of Anthallan treatment.

\*\*) In [ ] parenthesis re examined cases only

The remaining forty-two patients each received a course of Anthallan. Two patients had a recurrence of symptoms, and received a second course of the drug, and all cases satisfy the diagnostic criteria of hyperesthetic rhinitis. Many of the cases were patients at the Vanderbilt Clinic for a number of years and repeated studies by the staff, or by personal physicians, had established the presence of specific sensitivities in some of these cases.

The individual therapeutic results are surveyed in Table II A-C. Every change in the nasal manifestations observed during the period of treatment with Anthallan can be attributed to the influence of the drug. In all cases the Anthallan treatment period was considerably shorter than the period during which the manifestations had existed.

The percentage distribution of improvement obtained during Anthallan treatment is surveyed in Table III, upper part. In addition the results observed during Anthallan administration are compared in Table III, lower part, with those recorded after termination of the treatment. Only four cases were failures, including all degrees of improvement up to 24 per cent, a very low number, being less than 10 per cent of all the cases. The percentage of patients experiencing complete or practically complete relief from symptoms amounted to about 36 per cent\* during the course of therapy. An improvement of 70 per cent or more occurred in 56 per cent of the cases at the end of Anthallan treatment. This result persisted as far as could be judged from most of the patients who were available for reexamination at various post-treatment periods. The persistency of the result obtained during Anthallan treatment is shown in the lower part of Table III. Only about 30 per cent of all cases showed any tendency to relapse after two post-treatment examination periods, of one month or more, and even in these cases a considerable degree of improvement was still retained. In other words, there was never a case showing a complete relapse (except Case No. 24 which is reported in detail later). On the average, the improvement observed about 7 weeks after discontinuation of the drug compares favorably with the improvement shown at the end of the Anthallan period. The fact that there is an undeniable degree of persistence of the beneficial effect of Anthallan for a period after the administration is discontinued adds to the value of this drug.

The results were obtained within periods of treatment of an average length of 21 days. In 7 cases the treatment periods were considerably shorter, 7 to 14 days. Frequently, the degree of improvement recorded at the end of the Anthallan treatment period could be observed within the first 4 or 5 days of therapy.

The usual dose required to obtain these improvements was 6 capsules (each capsule 0.085 gm.) daily during the first week of treatment,

\* Varying according to whether the estimate is based upon Complaint or the comprehensive Medical Estimate.



Table IVB—LABORATORY STUDIES

<i>Blood Cell Count</i>										
<i>Case</i>	<i>Polym</i>		<i>Lymph</i>		<i>Baso</i>		<i>Monoc</i>		<i>Eos</i>	
	<i>%</i>		<i>%</i>		<i>%</i>		<i>%</i>		<i>%</i>	
	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>
1	59	50	36	41	0	1	4	7	1	1
2	56	51	33	33	0	1	7	8	7	7
3	61	61	25	26	1	0	5	6	8	7
4	74	72	0	25	0	0	9	3	17	0
5	52	64	33	28	0	0	9	5	6	3
6	49	59	40	29	1	1	5	5	5	6
7	78	71	16	25	1	2	5	2	0	0
8	53	54	23	30	1	0	8	3	15	13
9	65	—	27	—	0	—	7	—	1	—
10	48	—	35	—	1	—	7	—	6	—
11	57	—	26	—	1	—	7	—	9	—
12	53	—	36	—	0	—	6	—	3	—
13	66	59	24	29	0	1	4	6	6	5
14	45	61	35	29	2	0	7	3	9	7
15	60	65	28	22	0	1	11	9	1	3
16	83	—	12	—	0	—	5	—	0	—
17	—	—	—	—	—	—	—	—	—	—
18	58	59	32	26	0	0	6	2	4	13
19	—	—	—	—	—	—	—	—	—	—
20	44	71	37	24	0	0	9	1	10	4
21	41	54	45	35	1	0	2	6	11	5
22	—	—	—	—	—	—	—	—	—	—
23	66	57	24	36	1	1	5	5	4	1
24	60(22)	55	28(22)	35	1(22)	1	4(22)	5	7(22)	4
25	44[17]	51[17]	44[17]	46[17]	0[17]	0[17]	7[17]	1[17]	5[17]	2[17]
<hr/>										
Total	1274	—	42	—	11	—	139	—	135	—
	[966]	1014	[503]	519	[9]	[9]	[107]	[77]	[116]	[79]
Average	58	—	29	—	0.5	—	6	—	6	—
	[57]	[60]	[30]	[30]	[0.5]	[0.5]	[6]	[4.5]	[7]	[5]

a Test before Anthrallan treatment

b Test near end of Anthrallan treatment

\*\*) In [ ] parenthesis re examined cases only

Table IV—LABORATORY STUDIES

Case	Blood Chemistry				EKG	
	Glucose mg%		VPA mg%			
	a	b	a	b	a	b
1	91	90	20	37	—	—
2	99	83	20	15	normal	normal
3	93	—	20	—	LD*)	no change
4	87	—	22	—	normal	normal
5	86	90	21	21	normal	normal
6	90	92	19	18	—	—
7	85	86	22	25	normal	normal
8	92	88	23	24	normal	normal
9	86	—	25	—	—	—
10	96	—	23	—	—	—
11	86	—	21	—	normal	normal
12	96	—	28	—	—	—
13	95	103	20	23	—	—
14	—	81	—	22	—	—
15	92	78	19	21	normal	normal
16	89	89	20	20	normal	normal
17						
18	93	114	29	26	normal	normal
19						
20	71	98	18	23	SA*)	no change
21	85	83	21	24	normal	normal
22	95	96	22	21		—
23	94	87	20	25	RD*)	no change
24	97(22)	91	34(22)	34	normal	normal
25	99[17]	91[17]	25[17]	23[17]	normal	normal(15)
Total**)	1997		501			
	[1453]	[1540]	[362]	[402]		
Average	90		23			
	[90]	[90]	[23]	[24]		

a Test before Anthallan treatment

b Test near end of Anthallan treatment

\*) LD—Left Axis Deviation

RD—Right Axis Deviation

SA—Sinus Arrhythmia

\*\*) In [ ] parenthesis re-examined cases only

Table V—INFLUENCE OF ANTHALLAN UPON NASAL SMEAR EOSINOPHILES AS COMPARED WITH BLOOD EOSINOPHILES

No of Case	Eosinophiles Nasal Smear*)		Eosinophiles Blood Count	
	a	b	a	b
1	2	2	1	1
2	7	7	7	7
3	0	0	8	7
4	2	2	17	0
5	2	0	6	3
6	0	0	5	6
7	0	0	0	0
8	2	0	15	13
9	2	2	1	—
10	2	2	6	—
11	0	1	9	—
12	0	0	3	—
13	7	7	6	5
14	7	10	9	7
15	10	0	1	3
16	0	10	0	—
17	7	7	—	—
18	10	2	4	13
19	10	10	—	—
20	7	7	10	4
21	10	2	11	5
22	10	2	—	—
23	10	10	4	1
24	10	10	7(23)	4
25	10(25)	7(25)	5[16]	2[16]
Total**)	127	100	135	—
	—	—	[109]	[81]
Average	5	4	6	—
	—	—	[7]	[5]

a Test before Anthallan treatment b Test near end of Anthallan treatment

\*) Explanation of Rating of Nasal Smear

Rated as  
0

None seen

Between one and four per field from at least six oil immersion fields in separate areas of the slide

2

Between five and nine, as above

7

Ten or more, as above

10

\*\*) In [ ] parenthesis re examined cases only

this dose varied during the subsequent weeks between 3 capsules and 12 capsules daily according to clinical response. The dose did not have to be varied to any degree according to the age or sex of the patient. Altogether the average dose was about 7 capsules daily.

A collateral study of the clinical toxicity of the drug was carried on in the first twenty-five cases by laboratory studies of the blood count, urinalysis, blood chemistry, and nasal smear both before and after treatment. Electrocardiograms were taken before and at the end of Anthallan treatment in representative cases. During the weekly clinical examinations special attention was devoted to any symptoms or signs of side-effects of the drug, such as headache, vertigo, nausea, vomiting, diarrhea and skin rashes.

These laboratory tests and clinical observations were made during the course of Anthallan treatment to determine whether the drug in any way influenced the patient's normal picture. The results of these tests are shown in Table IV and Table V. Table IV indicates that glucose and NPN determinations, as well as hemoglobin, blood counts, urinalysis and electrocardiograms all remain essentially unchanged during and following treatment with Anthallan. Kline tests were also carried out routinely.

A comparison between nasal smear eosinophiles and blood eosinophiles, as recorded in Table V, showed no consistently parallel influence of Anthallan.

Clinical observations of possible toxic symptoms were essentially negative. Only 2 patients reported some side-effects during the period of treatment with Anthallan. One patient developed, at the end of the second week, a transitory fine macular rash which disappeared in 24 hours. One other patient developed diarrhea when taking 6 capsules daily, but was relieved by decreasing the dose to 4 capsules daily.

*Case Reports.* The following three cases are typical of those treated during this study.

*Case No. 3.* C.C., a 13 year old white schoolgirl of Spanish extraction complained of daily attacks of sneezing, watery nasal discharge and intermittent nasal obstruction during the past 17 months. All tests of foods and inhalants made in the allergy clinic were reported negative. The symptoms were aggravated in the morning, by changes in temperature, and during the winter months.

Physical examination of the nose and throat showed that there was

no mechanical obstruction to breathing, but that the nasal mucosa was paler than normal, was bathed in clear watery nasal discharge, and was thickened. Roentgenogram and clinical study of the nasal sinuses failed to show any evidence of infection. Blood count, blood chemistry, blood serology, urinalysis, and electrocardiograms were normal.

Sixty capsules (5 grams) of Anthallan were administered for 13 days. At the end of the treatment period the patient reported complete relief of symptoms. Physical examination of the nose showed that the mucosa appeared normal. All laboratory examinations were repeated, and no significant change was found (see tables). The patient experienced no objectionable signs or symptoms during the treatment period. Four reexaminations made during the first 9 months of the post-treatment period showed that the patient remained symptom free.

*Case No. 20 G L*, a 12 year old Negro schoolgirl, complained of daily attacks of itching of the nose and throat, associated with sneezing, watery nasal discharge and almost continuous nasal obstruction. All symptoms were aggravated by damp weather. The patient did not associate her symptoms with any infection, activity, food, wearing apparel, or inhalants. Nose drops gave temporary relief. No skin testing for allergens had been performed.

Physical examination shows the nasal cavity to be filled with watery secretion, and the mucosa to be pale and boggy. The septum was deflected, with a spur in the right inferior meatus. There was no other mechanical obstruction. Laboratory studies, and roentgenograms failed to show any evidence of infection.

After 35 capsules (4 gm) of Anthallan were administered during 7 days, the patient stated that she was completely relieved of all symptoms, and physical examination confirmed this statement. The routine laboratory examinations made before and after the treatment showed no variation from normal (see tables). Five reexaminations were made in the first 10 weeks of the post-treatment period, and the complete relief from symptoms continued.

*Case No. 24 F H*, a 37 year old baker of German extraction, complained of very severe attacks of sneezing, watery nasal discharge, and almost total nasal obstruction. He had been tested and was found sensitive to wheat and rye flour, and during the eight-hour work day in the bakery the symptoms were aggravated, but he was never completely relieved of symptoms during the 16 hours of the day that he was not

in contact with the flour. Desensitization gave no relief, but nose drops gave temporary relief. The severity of the symptoms increased during the humid weather.

Physical examination showed the presence of a slight conjunctivitis. Clinical study and roentgenogram of the sinuses failed to demonstrate any infection. There was extreme pallor of the nasal mucosa which was bathed in a tenacious clear secretion. There was also marked swelling of the mucosa but no polypoid change was seen. There was some deflection of the nasal septum without mechanical obstruction of the breathing space. A routine laboratory study showed normal values for blood count, blood chemistry, serology, urinalysis, and normal electrocardiograms.

Anthallan was given at the rate of 35 capsules the first week, 56 the second week and 70 the third week. During this period the patient continued to work in the bakery at his usual job. There was a steady improvement in the physical signs and symptoms during the 21 day period during which he took a total of 161 capsules (13.7 gm). No objectionable symptoms or side-effects were experienced, and laboratory studies repeated at the close of the treatment showed no significant change (see tables).

The patient and the observers agreed on the estimate that about 90 per cent relief of symptoms occurred during the administration of the Anthallan. During the first 6 weeks of post-treatment observation the patient continued his work as a baker with a gradual return of symptoms about 5 weeks after completion of Anthallan course. However he estimated that 75 per cent of the improvement originally gained was maintained. During the seventh week all of his symptoms returned to their full intensity, and he returned for a second course of treatment. All of the physical findings were present on the second as on the first examination.

Anthallan was again administered, and after 18 capsules taken during 3 days the symptoms were again relieved, to the extent of about 90 per cent. During a period of 28 days he took 158 capsules (12.9 gm) and has experienced about 100 per cent relief.

Three other cases\* are mentioned briefly because they illustrate the necessity of accurate diagnosis of associated conditions. One patient was a woman fifty-six years old who complained of the symptoms and

\* Not treated in the Vanderbilt Clinic Series

had the signs of a non-seasonal hyperesthetic rhinitis. Careful questioning showed that the onset of the symptoms coincided with the date of her son's sailing overseas with the Army, and the discussion precipitated hysterical weeping and an episode of hyperesthetic rhinitis. The patient was not accepted as suitable for Anthallan administration, as it was felt that the symptoms were entirely psychic in origin. However, 150 capsules of Anthallan were administered in 21 days without any effect whatever either good or bad.

A second case was a telephone operator 32 years old who complained of the symptoms and had the typical signs of non-seasonal hyperesthetic rhinitis for a period of 3 months. No sign of infection was found in the upper respiratory tract. Anthallan was administered for 3 weeks, a total of 168 capsules, without relief. At this time the patient mentioned that she was having some pelvic pain without any menstrual disturbance. Gynecological examination revealed an ovarian cyst measuring 8 cm. in diameter. The cyst was removed, and all nasal symptoms were relieved at once.

The third case was the sixth of the inconclusive cases listed above. Through an error, Anthallan treatment was begun before roentgenogram and nasal smear reports were made. The administration of Anthallan for 1 week had no effect on the nasal symptoms, which had been present for 10 years. After bilateral purulent maxillary sinusitis was demonstrated by the roentgenogram and by nasal smear, repeated bilateral lavage of the maxillary sinuses relieved all symptoms in 1 week.

These 3 cases illustrate the type of patient in whom failure has occurred. Patients in whom the signs and symptoms of hyperesthetic rhinitis are due to infection, to psychic disturbances, or to ovarian dysfunction will not respond to the administration of Anthallan.

#### SUMMARY

A study of the therapeutic usefulness and safety of the drug Anthallan was conducted in 42 cases of seasonal and non-seasonal hyperesthetic rhinitis. When Anthallan treatment was started, all patients had suffered from their disease continuously for periods of time averaging 506 days and varying between 11 days and 5 years. These patients had shown relief of only short duration in response to the customary methods of treatment given to the patients before they were treated with Anthallan. In 40 out of 44 courses (90 per cent) of treatment with

Anthallan a beneficial influence of the drug was observed. The improvement varied between 25 per cent and 100 per cent subjectively and objectively, as evaluated by a rigid schedule of numerical ratings of all the subjective and objective manifestations involved. The persistence of the improvement recorded at completion of Anthallan treatment was observed over an average post-observation period of 50 days (minimum 7 days, maximum 248 days). Laboratory studies and clinical examinations did not indicate any harmful effect produced by the treatment with Anthallan.

### CONCLUSIONS

The results of this study show that Anthallan, when used in doses of 3 to 12 capsules daily over a period of 7 to 35 days by patients selected according to the diagnostic criteria suggested in this study, is a useful drug for obtaining relief in a high percentage of cases of seasonal and non-seasonal hyperesthetic rhinitis, and that Anthallan can be used with complete safety.

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# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



JULY 1946

## CHEMOTHERAPY IN MALARIA\*

JAMES A. SHANNON\*\*

Associate Professor of Medicine, College of Medicine, New York University  
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Most of the recent advances in the chemotherapy of the malarias can be presented in the form of a commentary on the program of studies carried out under the auspices of the Office of Scientific Research and Development during the past four years. The studies were initiated in 1941 through the agency of the Committee on Medical Research with the aid of committees set up in the Division of Medical Sciences of the National Research Council.<sup>1,2</sup> The committees concerned with malaria underwent changes with the progressive expansion of the scope of the studies until, in the winter of 1943-44, the present program was evolved under the sponsorship of the Board for the Coordination of Malarial Studies and its various Panels. The Board is a cooperative endeavor and involves the participation of the Committee on Medical Research, National Research Council, Army, Navy, United States Public Health Service, and a group of investigators in civilian institutions under con-

\* Presented at the Eighteenth Graduate Fortnight of The New York Academy of Medicine, October 18, 1945.

The information contained in this paper is largely derived from work now sponsored by the Board for the Coordination of Malarial Studies and carried out by investigators of various institutions through contracts between them and the Office of Scientific Research and Development which were recommended by the Committee on Medical Research.

\*\*Now Director, The Squibb Institute for Medical Research, New Brunswick, N. J.

tract with the Office of Scientific Research and Development

The primary purpose of the investigations has been, at all times, to satisfy specific needs of the armed services. Information was required which would permit the better management of the malarial hazard first, as a factor of operational significance to combat troops in hyperendemic areas, and second, as a problem relating to the maintenance of good health of troops while they were in and after they had been removed from such an area. It was apparent from a consideration of these needs that initially, considerable work must be performed with antimalarial agents already available so that they could be used to the best advantage. However, it also seemed likely, that advantages would accrue were new and more effective antimalarials developed. More specifically, it was hoped that among the newer agents there would be one or more which would either prevent malarial infections or effect definitive cures at well tolerated dosage.

The direction of the early clinical work (1942-1943) was conditioned largely by the early loss to the United Nations of their normal sources of supply of quinine and by the lack of an adequate stockpile. Those who were intimately concerned with the malarial problem during the first year of the war will recall the gravity of the situation. The worry which was incidental to the lack of an adequate supply of quinine was enhanced by the preliminary reports from the field which carried the suggestion that quinacrine was of little use in the suppression and treatment of the malarias and that pamaquin as then used had little value in the cure of vivax malaria.

*The Investigation of Quinacrine* Quinacrine was said to be unable to produce a prompt termination of the clinical attack, more particularly, in falciparum malaria, much less a cure in either falciparum or vivax malaria. In addition, it was reported to be both highly toxic and relatively ineffective when used as a suppressive. These experiences caused many medical and line officers to believe that the control of malaria by quinacrine was not practicable. The clinical results were at such variance with reports in the literature<sup>3</sup> that an uncertainty existed in the minds of some as to the chemical identity of German and American quinacrine. This uncertainty was sufficiently serious to require the services of a number of chemists, pharmacologists and clinicians, the integrated efforts of which established the identity of the two products by the summer of 1942.<sup>4</sup> Even so there was a growing belief

that quinine was the only known antimalarial agent of consequence, that such of it as was available must be used sparingly,<sup>5</sup> and that a substitute for quinine, with all its limitations, was not only highly desirable, but urgently needed

The initial confusion concerning the therapeutic efficacy of quinacrine resulted from the lack of information which would permit its use in a rational manner. Empirical dosage schedules had been established at an earlier date and were generally used by the services.<sup>6</sup> These were based upon studies performed in the 1930's on groups of individuals with varying degrees of acquired immunity.<sup>3</sup> The dosage schedules which were found to be effective in such individuals are now known to be generally ineffective when applied to those who are wholly susceptible to these diseases. Furthermore, the recommended dosage regimen of suppressive quinacrine therapy brought into sharp focus the gastrointestinal irritation which frequently accompanies the oral administration of doses larger than 0.1 gram for suppressive purposes.

It is now established that quinacrine is a generally useful and highly effective antimalarial, quite superior to quinine in most situations.<sup>7</sup> This important advance in our knowledge resulted from the development of chemical methods for the estimation of quinacrine in biological fluids and tissues<sup>8-9</sup> and the use of these methods in studies which defined the antimalarial activity and physiological disposition of the drug.

It was first demonstrated in the winter and spring of 1943 that the inherent antimalarial activity of quinacrine is high and is related to its concurrent plasma concentration,<sup>10</sup> and that quinacrine is very extensively localized in the tissues of the body and degraded and excreted at low rates. It seemed reasonable to believe that the efficacy of suppressive quinacrine therapy would depend more upon the total dosage administered per week than upon the specific pattern of the dosage regimen. It also seemed reasonable to believe that since a quick therapeutic effect only obtains when a high plasma quinacrine concentration is reached early in the course of therapy, the efficacy of quinacrine in causing an abrupt termination of a clinical attack would depend largely upon the amount of drug administered during the first 24 hours of therapy.<sup>11-12</sup>

These concepts were quickly translated into practical regimens of therapy which have been in use by the Army and Navy for some two years.<sup>13</sup> As the result of this experience it is known that effective sup-



pression of malaria in the adult requires the administration of 0.1 gram of quinacrine daily, also to derive the maximal benefit, the drug should be administered for some two weeks prior to entry into an hyperendemic area and for some weeks after the risk of infection no longer exists. Prompt control of the clinical attack in vivax and falciparum malaria and cure in the latter infection can be accomplished by the administration of 0.8 to 1.0 gram of quinacrine in divided doses during the first 12 to 18 hours of treatment and 0.1 gram three times daily for an additional six days, or, an equivalent amount in a shorter period of time.

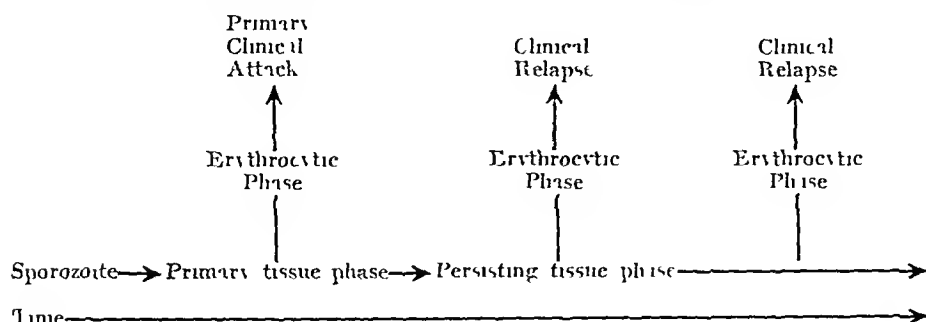
The establishment of quinacrine as a highly effective routine antimalarial permitted the clinical facilities of the civilian program to be directed towards the attainment of other objectives. This was because the proper usage of quinacrine had largely removed malaria from the field of tactical importance to the Services.

A consideration of the subsequent studies, which were aimed very specifically at the development of a curative agent in vivax malaria, requires a definite understanding of the specific limitations of quinacrine. It will prevent the inception of clinical falciparum malaria when given as a suppressive, and effect a prompt and definitive cure when the infection is once established. However, quinacrine will not prevent the inception of vivax malaria although it is highly effective in suppressing its clinical manifestations, and, it will not effect a definitive cure when the infection is once established. These two limitations are fundamental in nature. The drug has other limitations but these are of lesser importance. It is prone to cause gastrointestinal reactions when administered for suppressive purposes in single doses in excess of 0.1 gram. This is of some consequence since it increases the administrative burden of suppressive therapy, requiring as it does a daily dose of drug. The yellow staining of the skin which is a constant finding with quinacrine therapy may also be mentioned since it is an undesirable feature. Other toxic manifestations are too infrequent to warrant special attention at this time.

*The Search for new more Effective Antimalarials (Suppressives)*

An understanding of the biological basis for the most important fundamental limitation of quinacrine, i.e., its inability to cure vivax malaria, and the design of experiments to discover antimalarials not having a similar limitation require an appreciation of some of the important features of the biology of the malaria infections. The disease mechanisms

FIGURE 1  
PROPOSED SCHEME TO DESCRIBE THE UNDERLYING  
DISEASE MECHANISM OF VIVAX MALARIA



which underly the human infections may be assumed to parallel, in certain respects, those which have been described in some detail for several avian infections<sup>11</sup> A general outline of a mechanism which seems reasonable for vivax malaria<sup>12</sup> is presented in the accompanying figure (Figure 1) Consideration is not given to the sexual forms of the parasite, i.e., the gametocytes These have no importance in conditioning the clinical course of the disease in the individual patient

Such an outline assumes that, subsequent to the deposition of sporozoites by the mosquito, a tissue phase of the developing plasmodium is established and persists for a considerable period of time It is further assumed that lines of erythrocytic forms of the parasite are derived from the tissue phase as discrete episodes in the course of the disease These in turn are responsible for the initial attack and the parasitological and clinical relapses which are characteristic of vivax malaria The early portion of the disease mechanism in falciparum malaria appears to be similar to that of vivax malaria in all respects However, there is no need to assume the life history of the falciparum parasite also includes a persisting tissue form since this type of malaria does not systematically relapse If a persisting tissue form is present in falciparum malaria, then it poses no special therapeutic problem since, contrary to vivax malaria, the disease can be cured by a variety of chemotherapeutic agents which are also highly effective against the erythrocytic forms of the plasmodium

It will be appreciated from such a summary, that the malarial parasite has a rather complex life history within the human host when the infection is acquired naturally This involves several phases of develop-

ment each of which may be expected to differ from the others as to morphology, metabolic characteristics, and the cell type of the host within which it takes place. It will also be appreciated that potentially there are several types of antimalarial activity in the vivax infection. For convenience these may be designated as prophylactic if the action is on the sporozoite or the primary tissue forms of the plasmodium, as suppressive if on the erythrocytic forms or as curative if on the persisting tissue forms.

Each of these types of antimalarial activity may be examined separately. The testing for prophylactic or curative activity requires the use of mosquito induced malaria. The latter is further complicated by the need for a long term observation period before a final judgment can be made on the extent to which a given drug or a given dosage regimen is curative. However, suppressive antimalarial activity is amenable to simple and rather precise assay by the use of blood induced infections.<sup>15</sup> This type of infection has a more simple disease mechanism. It is established by the simple transfer of infected blood from a patient with an active infection and having only the erythrocytic phase of the disease, it permits the examination of the suppressive type of activity alone. It is important to note that the differences in suppressive and curative activities could be either quantitative or qualitative. Consequently, the development of an antimalarial with a high degree of curative action in vivax malaria could be approached with reason by more than one way.

One approach could be based upon an hypothesis which held the fundamental metabolic organization of the persisting tissue forms of *P. vivax* to be essentially the same as that of the erythrocytic forms of the plasmodium. Due to differences in their environments, the tissue form was assumed to be less susceptible to the antimalarial effect of drugs such as quinacrine. Accordingly, a reasonable approach to the development of curative agents appeared to lie in the direction of obtaining more active drugs as evidenced by their ability to exert an action upon the erythrocytic forms of the parasite, i.e., as manifested in the blood-induced infection. It was hoped that if the intensity of this type of antimalarial activity was sufficiently great in the case of any drug then it would not only interrupt the erythrocytic phase of the vivax parasites but would also obliterate the persisting tissue phase of a naturally acquired infection and so cure the disease.

Another approach could be based upon an hypothesis which held

the fundamental metabolic organization of the persisting tissue forms of *P. vivax* to be different from that of the erythrocytic forms of the plasmodium, at least insofar as the susceptibilities of their essential biological systems were concerned. Accordingly a chemotherapeutic agent might affect the tissue forms through an action which was qualitatively different from any which produced a dramatic effect upon the asexual forms in the erythrocyte i.e., the blood-induced infection had little value in the search for curative agents. In accordance with this hypothesis, it would be quite possible to miss a curative agent unless a number of representatives of each group of chemicals studied were examined for curative action. Compounds could then be selected for this type of activity because of special activities other than suppressive in the avian infections, or, they could be screened for curative action in the human *vivax* infection without prior experimental trial.

It was generally agreed in the fall and winter of 1943 that, sufficient evidence was not available for one to decide which of these two hypotheses was more reasonable. Consequently there was considerable discussion, as to whether blood-induced infections could be of value in a program, the end of which was the development of curative agents for *vivax* malaria. However, this type of infection was continued in use on a rather extensive scale, its use being based on the tentative acceptance of the reasonableness of the first working hypothesis. As a logical consequence and as the major effort at that time a systematic attempt was made to increase antimalarial activity in a number of the chemical series then under exploration and the best representative in each series was selected on the basis of information from blood-induced infections, and examined for curative action in mosquito induced *vivax* malaria. Actually the overall procedure adopted represented a partial compromise between the two working hypotheses. Certain of the compounds studied for curative action had relatively little suppressive action their selection being based upon two considerations. They were representatives of chemical series as yet untried for curative action and although they might have had little suppressive activity, the compound tested was better in this respect than the other members of the series examined. In addition any compound showing a special type of activity in the avian infections, such as curative or prophylactic was also tried for curative action in *vivax* malaria.

The advantages of this approach, at that stage of the program were

three First, it was believed likely, with the leads then available, that suppressive antimalarial activity could be increased many fold in several different types of compounds and, as the result of this effort, compounds would shortly become available with which to test the correctness of the first working hypothesis Second, it would permit the study of a number of chemical series, as yet unexamined, for their possession of curative action and perhaps establish a correlation between special activities in avian infections and curative activity in vivax malaria Third, it seemed reasonable to suppose that this approach to the problem would result in the development of antimalarials superior to quinacrine although they might have the same fundamental limitations The third possibility was important It was desirable to have available antimalarials other than quinacrine should the long-term continuous administration of quinacrine to the human be accompanied by toxic manifestations which at the time could not be predicted

It was early demonstrated beyond doubt that the suppressive antimalarial activity of a compound, when measured in a single avian infection, may have little prediction value for the situation obtaining in the suppression of peripheral parasitemia in the human malarias\* It was later demonstrated that the sum total of the information, when derived from the study of the activity of a compound or series of compounds in several avian infections using several avian hosts, does have fair prediction value in the selection of compounds for trial as suppressives in the human malarias Lastly it was demonstrated, within the compounds studied, that none had higher antimalarial activity of a suppressive nature in both human infections that had been observed in at least one of the avian infections\*\* This information was accumulated incidental to the survey of a very large number of compounds (ca 14,000) for activity in the avian infections, the survey of a limited number of compounds (ca 65) for suppressive activity in the human infections and a selected number of the latter group (ca 20) for prophylactic and curative action in vivax malaria

Out of these extensive studies no compounds were developed with prospects of being useful as curative agents in vivax malaria although

The data available on antimalarials at the beginning of the program and those from allied fields of chemotherapy led Doctor E. K. Marshall, Jr., Chairman of the Pharmacological Panel, to this conclusion

\*\* The substantiation of these general concepts was as the result of the combined efforts of all Office of Scientific Research and Development contractors on both the pharmacological and clinical levels The experimental facts themselves will be contained in a monograph entitled 'A survey of antimalarials 1941-1946' edited by Doctor F. Wiselogle and prepared by The Office for the Survey of Antimalarial Drugs This monograph should be available by the summer or fall of 1946

several have unquestioned advantages over quinacrine and quinine. For example, a plasma quinine concentration of 5 mg per liter maintained for four days terminates a blood induced infection or a clinical attack of a mosquito induced infection due to the McCoy strain of *P. vivax*.<sup>10</sup> An equivalent effect will be produced by 30 micrograms per liter of quinacrine.<sup>10</sup> However, plasma concentrations of quinine in excess of 12 mg per liter and of quinacrine in excess of 150 micrograms per liter are not generally well tolerated.

Of the newer compounds developed during the fall and winter of 1944-1945, there is one (SN-7618)\* which is rather well tolerated at dosage schedules which produce plasma drug concentrations some 30 times those required to terminate the clinical attack.<sup>16</sup> Others, where activities have been placed less precisely in terms of plasma drug concentrations, can be administered in daily doses many many times those required to produce a demonstrable antimalarial effect. Nevertheless, these agents have nothing to offer as curative agents in *vivax* malaria. It may be concluded from these observations that the major working hypothesis selected for trial in 1943 in the attempt to develop curative agents in *vivax* malaria is not correct.

Before considering the next phase of studies it will be of some interest to take note of the potentialities of certain of the agents which, at least to some extent, are by-products of an unsuccessful attempt to produce a curative agent for *vivax* malaria. Among the more promising compounds are some which may be expected to effect complete suppression when administered once weekly in a well tolerated dose. They will also effect an abrupt termination of a clinical attack of *vivax* and a cure of falciparum malaria when administration is limited to one or at most, two days. None of these highly effective agents has, as yet, been fully exploited. However, information is at hand which permits the prediction that they will constitute a relatively simple means for the complete control of malaria in many areas due to the lessening of the administration problem of suppressive therapy as compared to quinacrine. They may also, in specific areas, contribute to the eradication of the malarias through their ability to curtail transmission of the disease. Exploration of the advantages to be derived from the use of some of these newer agents is now under way.

\* SN 7618 is 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline. Several closely related compounds have comparable activity.

*The Search for More Effective Antimalarials (Cinative)* Of importance to the attainment of one of the ultimate objectives of the program was the conclusion that a simple increase in antimalarial activity as evidenced by an effect against the erythrocytic forms of the parasite cannot, *per se*, be expected to lead to curative drugs for vivax malaria. The obtaining of this information marked the beginning of the present stage of the malaria studies. This has been characterized by the direct approach to the problem of devising curative agents which are now assumed to require qualitatively different actions than those which are simply reflected in a reduction of peripheral parasitemia in vivax and falciparum malaria. These studies are proceeding in several laboratories and with some prospect of success.

A serious obstacle to success in this endeavor stems from the fact that, with our present knowledge, it is not possible to use the experimental avian malarials effectively to screen compounds prior to their selection for trial as curative agents in vivax malaria. Drugs have been developed which possess prophylactic and/or curative action in one or another of the avian infections but, generally speaking, these actions are not a reflection of a similar action in vivax malaria. Actually, there is, as yet, no general correlation between these special actions in the avian infections and comparable action in the human infections. The promise that curative drugs will eventually be found stems solely from the recent confirmation of the earlier studies on the curative action of pamaquin, an 8-aminoquinoline.

It seems reasonably certain that the older investigations on the antimalarial activity of pamaquin led to conclusions which are essentially correct.<sup>17</sup> That is, pamaquin, when administered at high dosage, has a curative action in vivax malaria when administered concurrently with quinine over a long period of time. This is a fact of importance. It demonstrates that the persisting tissue forms of the plasmodia which are held to be responsible for the relapse in vivax malaria are subject to the lethal action of a drug to which the type of host cell within which they reside is not also generally susceptible. Furthermore, the curative action of pamaquin makes available a specific lead towards the synthesis of better tolerated curative agents.

This synthetic lead is now being explored extensively. It did not receive attention earlier in the program for three reasons. It was known that pamaquin analogs had received systematic study by the Germans,

French, and Russians, both before and after the development of pamaquin, and no better drug had been announced. It was also known that pamaquin and many of its analogs possess seriously toxic effects when administered at a dosage well below that which is generally curative. Finally, it was hoped that a curative agent might be found in other series of substances which were characterized by lesser toxicity. It was not until the last possibility seemed unlikely, at least in the near future, that it was deemed advisable to embark upon an extensive study of 8-aminoquinolines.

It is now known that previous exploration of the 8-aminoquinolines was inadequate to be certain that pamaquin is the best drug to be derived from this series. Furthermore, the careful study of the antimalarial activity and toxicity of pamaquin and a selected series of 8-aminoquinolines seems to indicate that such an exploration will be profitable. A consideration of what has been done with other chemical series whereby one or another aspect of antimalarial activity has been greatly increased without a comparable increase in toxicity, makes the prospect of obtaining a useful agent from this group of substances rather bright though highly speculative.

Should it happen that generally useful curative agents for vivax malaria are contained in the series of 8-aminoquinolines, this will make an interesting chapter in the development of antimalarial agents. Pamaquin was first used on a very extensive scale in the late 1920's. It was said, on the basis of preliminary studies, to possess some suppressive effect upon the erythrocytic phase of vivax malaria, as well as a curative action in this disease. It was also said to have little or no suppressive effect upon the erythrocytic phase of falciparum malaria but a dramatic effect upon the gametocytes of the plasmodium responsible for this infection. In addition it was said to be a true prophylactic in each infection.

Shortly after the drug was available for large scale experimental use it became apparent that the dosage recommended in the earlier studies could be expected to produce widespread and seriously toxic effects. However, the extent of the toxicity was not appreciated at a sufficiently early date to prevent the organization of reasonably well controlled trials to assay the curative action of pamaquin in vivax malaria.

It was common practice at that time to treat both vivax and falciparum malaria with full therapeutic doses of quinine about 20 grams



daily, for some 14 to 21 days. Consequently, when pamaquin was tested it was also administered for this period of time. It was demonstrated quite early that a combination of concurrently administered pamaquin and quinine is superior to the administration of either drug alone. For example, in one series<sup>17</sup> there was observed 75 per cent relapses in an eight weeks period with quinine alone, 25 per cent with pamaquin alone and essentially none with a combination of the two antimalarials. The dosage of pamaquin in these studies, calculated as the hydrochloride was as low as 40 mg daily in many patients. It is possible that such a dosage regimen would have come into general use despite the toxic effects of the pamaquin except for the discovery and limited exploration of quinacrine which occurred about this time.

It was found, with quinacrine, that little advantage is derived from the administration of quinacrine beyond a seven day period of treatment at 0.1 gram three times a day in population groups having a fair degree of immunity. As a reaction to this finding, the belief gained credence that quinine administration might also be curtailed to a similar period with advantage. This belief together with a growing appreciation of the toxic hazard of pamaquin led to a curtailment in the duration of the administration of quinine as well as a lowering of the pamaquin dosage commonly used. It is not surprising then, that the publications of the League of Nations recommended that combination pamaquin and quinine therapy be limited to seven days with the daily dose of pamaquin no higher than 30 mg of the hydrochloride. The increase in the toxicity of pamaquin when administered concurrently with quinacrine led to the adoption of a convention whereby pamaquin was administered in similar dosage but for only five days and separated from quinacrine administration by a three day drug free interval. It is now known that pamaquin administered at such a dosage and in such manner has little to offer as a curative agent in vivax malaria although it is a highly effective gametocidal agent. It seems likely that the early studies with pamaquin produced a different therapeutic result because the dosage was usually higher, administration was for a longer period of time and the drug was administered concurrently with quinine. However, all three features were lost sight of in the years between 1931 and 1941 so that, the early recommendations for the use of pamaquin by the services were not of the type that would be expected to yield a significant proportion of cures.<sup>6</sup>

Work during the past year has retraced these steps and it is believed that the examination of the curative action of the 8-aminoquinolines is again on a sound experimental basis. However, progress towards the ultimate goal of these studies will be slow since, at the moment, it is necessary to restrict the primary examination of compounds in this series for curative action to human experimental material.

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## SOME EFFECTS OF THE RICE DIET TREATMENT OF KIDNEY DISEASE AND HYPERTENSION\*

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KIDNEY cells can be kept "alive" for a few hours in the Warburg apparatus and their chemical reactions examined in a rather simplified set-up.<sup>1</sup> Tissue slices thin enough to permit optimal diffusion are suspended in salt solutions, serum or exudate. The concentration of oxygen, carbon dioxide, sodium bicarbonate, sugar, aminoacids, ketoacids, lactic acid, etc., in the suspension milieu can be quantitatively controlled. Factors such as the rate of arterial and venous blood flow, the lymph flow, and the excretion of urine do not complicate the experiment. From one five-minute period to another one can measure manometrically what these isolated kidney cells do under varying conditions.

Like all other animal tissue, kidney cells have two main sources of energy, oxidation and fermentation. Values of about 10 are given in the literature for  $\text{BO}_2$  and  $\text{QM}_{\text{N}_2}$  of human kidney cortex,<sup>2</sup> i.e., the approximate amount of oxygen used for oxidative processes by 100 Gm of fresh kidney substance would be about 5 liters in 24 hours, the approximate amount of lactic acid formed anaerobically in the same time would be about 2 Gm.

If in the course of a disease, renal tissue is destroyed and replaced by a scar, obviously the only metabolic reactions to be found will be those of the scar tissue and no longer those of the kidney cells. Between normal and completely destroyed cells, there are as far as disturbances of cellular metabolism are concerned, the following possibilities:

- 1 The cells are uninjured, but metabolize in a pathological environment
- 2 The cells are injured, but the environment in which they metabolize is normal

\* From the Department of Medicine, Duke University School of Medicine, Durham, N. C. Read January 15, 1946 before the Section of Medicine of The New York Academy of Medicine.

TABLE I—CHANGES IN CHEMICAL COMPOSITION  
OF 'INFLAMMATION FLUID

	<i>Serum</i>	<i>Fluid from Sterile Blister of Skin (Normal person)</i>
Oxygen (mm Hg)	110	6
Sugar (mg/100 cc)	90	6
Lactic Acid (mg/100 cc)	10	125
Bicarbonate ( $10^{-3}$ molar)	25	9
PH	7.4	6.3

### 3 The cells are injured and metabolize in a pathological environment

In order to learn something about the chemical composition of such a "pathological environment" we measured the metabolic reactions which take place during an inflammation. We produced sterile cantharidin blisters on the skin of normal people and of patients with various diseases and measured the metabolism of the leukocytes in the blister fluid and the chemical changes produced by them.<sup>4</sup> As Table I shows, the concentration of some biologically essential substances shows a decisive change during inflammation.

The next step was to determine what effects on the metabolism of kidney cells were produced by these environmental changes. We found the anaerobic splitting of sugar into lactic acid to be markedly dependent on changes of the sodium bicarbonate, sugar, and hydrogen ion concentration. The rate of oxidation was, to a large extent, independent of sodium bicarbonate, sugar, and PH, but was dependent on variations of oxygen concentration.

We could show further that the deamination of aminoacids and the formation of ammonia by slices of kidney tissue are inhibited by lowered oxygen concentrations. This applies both to the so-called "unnatural" d-aminoacids and to those naturally present in the plasma of man, rat, and rabbit, and in the tissue slices themselves.<sup>5</sup>

Besides the inhibition of the rate of deamination, which is reversible there is another effect of low oxygen concentration on kidney cell metabolism which causes irreversible changes. If we kept slices of

kidney tissue for about one hour in an oxygen free atmosphere and then re-established conditions of optimal oxygen concentration the cells were still able to deaminate aminoacids and to form ammonia but they had lost the ability to oxidize ketoacids<sup>6</sup> This means that by the removal of oxygen for a given time one can injure kidney cells selectively as to their oxidative reactions

The obvious question is What practical significance have these cellular physiological findings in the treatment of diseases in which renal metabolic dysfunction may play a role Some simple examples may show the trend of our reasoning Let us assume that the oxygen *supply* to any one kidney cell has been decreased by some pathological condition and that we are unable to increase it, still, it might be possible to increase the oxygen *concentration* by reducing the amount of work required from this cell, thus decreasing its oxygen demand Or let us assume that the rate of oxidation of ketoacids in any one diseased kidney cell is decreased, still, it might be possible to reduce the amount of ketoacid offered to the cell if we were able to remove from the diet those substances from which ketoacids are derived Deductions of a similar kind might be drawn from observation of the role played in renal metabolism by aminoacids, sugar, sodium bicarbonate, etc

It would be most desirable, of course, to substitute for the natural ferments that have been destroyed, extracts of animal kidneys, or even better, synthetic substances with the same chemical properties as those in normal kidney cells Unfortunately, such substances are not yet available

I have been asked to speak to you this evening about a less perfect approach, but one which has led to rather satisfactory results the compensation of renal metabolic dysfunction with the rice diet

The consensus of opinion at the present time is that dietary treatment is useful in kidney disease, but of little or no value in hypertension without obvious renal involvement Goldring and Chasis in 1944 summed up the prevalent view in their book on hypertension "The diet in uncomplicated hypertension requires no essential change from the normal"<sup>7</sup>

Compared to diets previously used in hypertension, the rice-fruit-sugar diet is rigid It contains in 2000 calories about 5 Gms of fat and 20 Gms of protein derived from rice and fruit, and not more than 0.2 Gm of chloride and 0.15 Gm of sodium<sup>8</sup>

TABLE II—SERUM CHOLESTEROL OF PATIENTS WITH  
HYPERTENSIVE VASCULAR DISEASE ON RICE DIET

(Mg per 100 cc of serum)

<i>Case</i>	<i>Before</i>	<i>After</i>	<i>Days</i>	<i>Case</i>	<i>Before</i>	<i>After</i>	<i>Days</i>
1	205	178	67	41	283	205	203
2	220	191	42	42	238	210	84
3	168	175	240	43	333	270	28
4	173	170	56	44	266	154	112
5	225	177	143	45	345	258	74
6	238	200	61	46	293	200	20
7	246	200	156	47	268	170	133
8	255	215	47	48	302	217	100
9	290	150	288	49	222	70	99
10	354	275	134	50	210	190	109
11	242	172	72	51	300	225	166
12	292	237	212	52	242	152	126
13	234	173	73	53	145	188	21
14	187	186	85	54	220	166	105
15	325	226	31	55	290	160	102
16	260	192	110	56	195	168	21
17	217	190	125	57	318	235	9
18	212	176	130	58	220	187	53
19	228	166	35	59	246	220	136
20	317	186	52	60	210	205	24
21	224	155	32	61	225	200	16
22	172	160	35	62	273	230	9
23	218	135	90	63	210	143	43
24	221	192	40	64	215	155	221
25	255	146	139	65	230	153	17
26	210	225	228	66	210	175	212
27	230	164	35	67	292	168	78
28	300	198	6	68	215	110	76
29	231	213	166	69	239	149	60
30	209	181	12	70	192	215	24
31	250	247	32	71	308	246	155
32	250	260	65	72	258	175	41
33	252	161	14	73	193	153	16
34	185	108	14	74	260	170	178
35	188	150	83	75	168	160	240
36	300	203	45	76	317	170	146
37	284	235	18	77	200	175	6
38	230	228	21	78	304	169	66
39	332	246	14	79	186	102	205
40	137	175	28				
				Average	243.2	185.9	
				Average Difference	57.3 mg		

It has been argued that this diet is nothing but starvation and that at least the "wear and tear quota" of 45 Gms of protein is needed to maintain protein equilibrium. This figure, however, has no other basis than the 7 Gms of nitrogen excreted per day by people who are fasting and represents only the body's effort to meet its caloric requirements by breaking down its own protein. The daily urinary nitrogen excretion of patients who have followed the rice diet for two months or more averages 2.26 Gms, which means that with a daily intake of little more than 15 Gms of protein due to the protein sparing effect of carbohydrates, the nitrogen equilibrium is maintained.<sup>9</sup> In fasting, the daily urea nitrogen excretion in the urine is about 5.5 Gms. The average daily urea nitrogen excretion in the urine of patients who have followed the rice diet for two months or more is 1.1 Gms.<sup>9</sup>

In fasting, the blood urea nitrogen concentration is higher than it is normally. In patients on the rice diet, the urea nitrogen concentration is below the level of normal (average of 6.6 mg per 100 cc of blood). In starvation, hemoglobin and plasma protein concentrations decrease, in patients on the rice diet, the hemoglobin and plasma protein levels are maintained.<sup>9</sup>

It has been argued that the restriction of fat in the rice diet is too rigid and that patients with hypertension should eat "well-balanced meals." On the other hand the relation between hypercholesterolemia and hypertensive vascular disease has been stressed repeatedly, especially with regard to vascular retinopathy, coronary disease, and arteriosclerosis. In a series of 79 patients with hypertensive vascular disease 53 (i.e., 67 per cent) had a cholesterol concentration of at least 220 mg per 100 cc serum at the beginning of the treatment. As Table II shows, the hypercholesterolemia decreased with the rice diet in 52 of the 53 patients, the average decrease being 74 mg per 100 cc serum, in 37 of these 52 patients, the cholesterol concentration became normal. The hypercholesterolemia increased in 1 of the 53 patients (from 250 to 260 mg). In 1 patient the cholesterol concentration increased from normal (210 mg) to a hypercholesterolemic level (225 mg).

It has been argued that the restriction of salt has no effect on hypertensive vascular disease. Therapeutic results such as those of Allen and Sherrill<sup>10</sup> and of Volhard<sup>11</sup> have been explained by Fishberg<sup>12</sup> on the assumption that salt-poor diets, because of their unpalatability lead to restriction of caloric intake and thus to reduction of the metabolic

TABLE III—CONCENTRATION (GM) PER 1000 CC OF URINE OF PATIENTS ON "NORMAL" DIET AND ON RICE DIET

	<i>Normal Diet</i>	<i>Rice Diet (after 2 months)</i>
Urea N	12	1.1
Chloride	6	0.1
Sodium	4	0.01
Potassium	2	3.0
Sodium/Potassium Ratio	2	0.003

rate. According to Page,<sup>13</sup> the effects obtained were due not to salt restriction, but to rest in bed, and the "psychotherapy of constant attention."

With the rigid restriction of sodium and chloride in the rice diet, the sodium and chloride excretion in the urine decreases to minimal amounts. In the urine of patients who have followed the rice diet for one month or longer, the average chloride concentration is about 100 mg, the sodium concentration about 10 mg, the potassium concentration about 3 Gms per liter, i.e., the potassium concentration is slightly higher than that in the urine of patients on an ordinary diet, the chloride concentration is decreased to about 1/60, the sodium concentration to about 1/400. The sodium-potassium ratio, which in the urine of patients on an ordinary diet is about 2, decreases on the rice diet to 0.003 (Table III).

Grollman and Harrison repeated some experiments with the rice diet, using rats with experimental hypertension, they confirmed our finding, that the rice diet leads to marked blood pressure reduction.<sup>14</sup> Since the hypotensive effect was not obtained when the strict rice diet was changed by the addition of NaCl (not of KCl), this hypotensive effect was ascribed by the authors merely to sodium restriction. Unfortunately, no sodium, potassium, or chloride determinations in blood or urine were made.

No matter which single factor in the rice diet is of greatest importance in compensating the various manifestations of renal metabolic or excretory dysfunction, it remains true that in 203 of 322 patients,



## TABLE IV

B 50182

White married man Born 1902 "Always healthy until 1939" Blood pressure checked at two year intervals since 1927 B P known to be normal in 1936

1939 Blood pressure elevated Treated with Barbiturates

March 1940 NEW YORK HOSPITAL B P 200-165/135-105

Retrograde pyelograms "Normal"

"Hypertensive vascular disease"

January 1941 PRESBYTERIAN HOSPITAL, NEUROLOGICAL INSTITUTE

"Hypertensive cardiovascular disease" B P 200/140

February 1941 ROCKEFELLER HOSPITAL B P 200/140

Variations 196-174/140-120

"Hypertensive vascular disease arterial hypertension"

Daily injections of Tyrosinase intravenously for 23 days Slight decrease in B P

Daily injections of Tyrosinase subcutaneously for 13 days Decrease in B P to 150/100

November 1941 B P 200/140

After one week, B P at previous level During Tyrosinase treatment B P 164/110

Because of severe shock-like reaction, Tyrosinase therapy discontinued

MASSACHUSETTS GENERAL HOSPITAL (Dr Smithwick)

Lumbodorsal sympathectomy  
(Dec 1941-Jan 1942)

# BLOOD PRESSURE DATA EKG

Admission Lying Standing

Dec 1941 Before sympathectomy 172/135 180/134 186/145 12-18-41 T<sub>1</sub> upright

Mar 1944, 26 mos after sympathectomy 204/144 196/140 150/123 12-29-43 T<sub>1</sub> upright

Beginning 1945 Therapeutical trial with Testosterone "Blood pressure higher"

March 31, 1945 DUKE HOSPITAL Admission 220/132

(All B P readings taken while lying)

March 31 - April 19, 1945 Average of 20 days in hospital on 1500 cal reduction diet B P 197/129

PSP (total excretion in 2 hours) 62%

Urea clearance 125%

T<sub>1</sub> diphasic Transverse diameter of heart 14.8 cm

April 20, 1945 Rice diet started

Averages

May 15-21, 1945 129/94

June 1, 1945 full time job resumed

July 1945 125/90

August 1945 120/87

September 1945 126/88

October 1945 129/87

November 1945 128/89

January 8-14, 1946 128/91

I<sub>1</sub> upright Transverse diameter of heart 13.9 cm

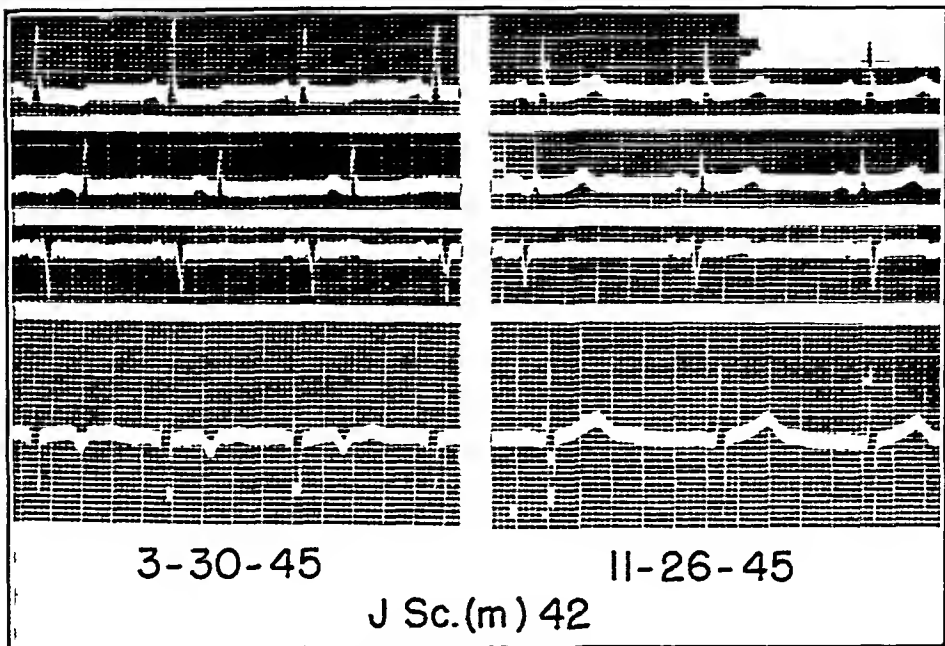


Fig 1 J S (m 42) "Hypertensive Vascular Disease" Rice diet since 4-20-45 No digitalis Diphasic I 1 has become upright

on most of whom other forms of therapy had previously been tried, the rice diet led to objective improvement

Of 100 patients with primary kidney disease, 65 per cent showed improvement on the rice diet. Of 222 patients where a diagnosis of hypertensive vascular disease was made, 62 per cent improved.

Those who question the value of diet in the treatment of hypertensive vascular disease say that in those patients who responded to the diet our diagnosis was probably incorrect. I think that in most cases the differential diagnosis presents no difficulties. Table IV shows the summary of a typical history.

It would not be right to use such a case as an argument against sympathectomy. I have seen marked blood pressure reduction following sympathectomy, in patients with severe hypertension, and I have seen patients whose blood pressure was not improved. But I do think that the sequence of surgical treatment and dietary treatment should be reversed since the treatment with the rice diet, if it proves to be ineffective, can simply be discontinued.

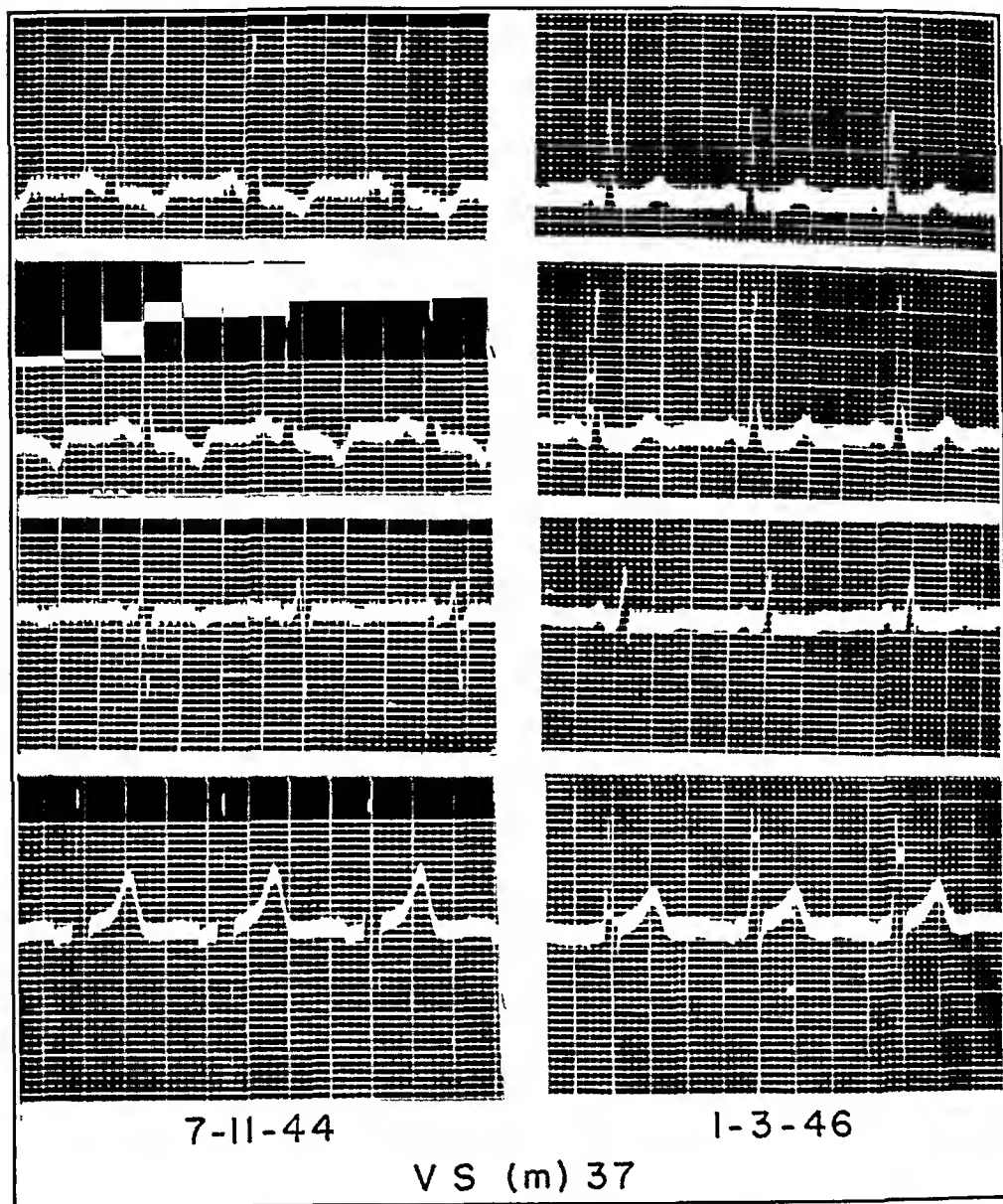


Fig 2 VS (m) 37 'Hypertensive Vascular Disease' Advanced retinopathy Rice diet since 8-16-44 No diuretics Change in electrical axis Inverted T1 has become upright

In the patient just mentioned, in spite of the sympathectomy, the electrocardiogram began to show myocardial involvement T<sub>1</sub> which in December 1941 and December 1943 was upright, had become diphasic by April 1945. With the rice diet, however, the diphasic T<sub>1</sub> reverted to normal (Fig 1)

We have studied the electrocardiographic changes in 100 patients

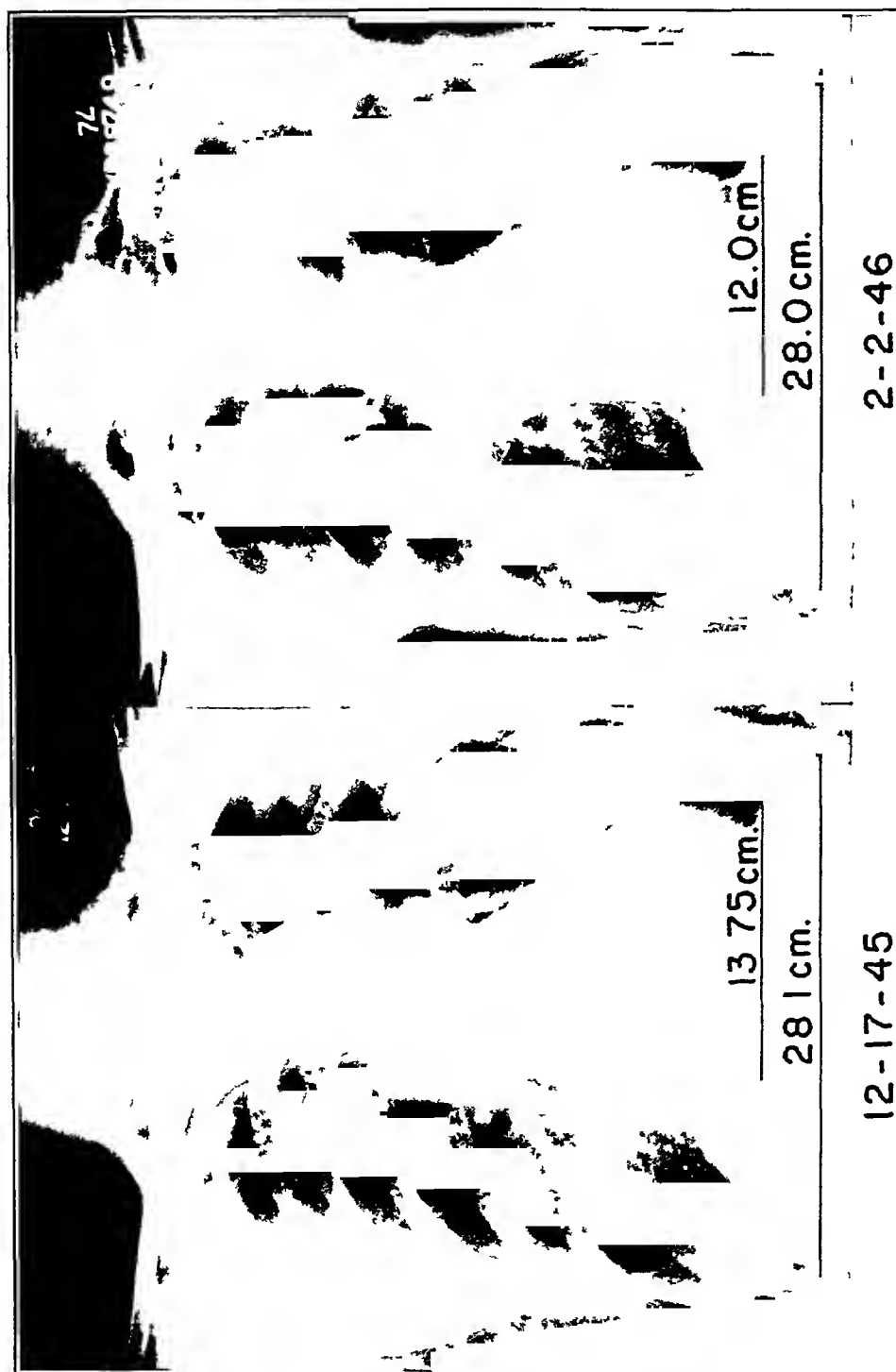


Fig. 3. McD. (m 62) Hypertensive Vascular Disease. Rice diet since 1-6-46. No digitalis. Reduction of heart size with change in transverse diameter of 11 per cent.

with hypertensive vascular disease, who have followed the rice diet for two months or longer. In 31 of these patients, the  $T_1$  waves were completely inverted before treatment. In 11 of these 31 patients,  $T_1$  became normally upright with the diet (Fig. 2). In no patient did the reverse occur. The shortest time in which a completely inverted  $T_1$  became upright was two months, the average was six months.

In 77 of 87 patients with hypertensive vascular disease, the heart became smaller in size (Fig. 3). The average change in the transverse diameter was 10.1 per cent. The average chest diameter decreased by less than 0.7 per cent.

In 10 of the 87 patients the heart became larger. In these the transverse diameter of the heart showed an average increase of 2.5 per cent. The average chest diameter increased by 0.54 per cent.

I am sometimes told that enlarged hearts in hypertensive vascular disease become smaller "spontaneously," that electrocardiograms became normal "spontaneously," and that papilledema, hemorrhages, and exudates in the retina disappear "spontaneously."

I have not been fortunate enough to see many of these "spontaneous" recoveries, but I have often seen blindness as a result of advancing vascular retinopathy and death from heart failure, myocardial infarction, renal insufficiency, or cerebral vascular accident in patients who were not willing to submit to any drastic form of treatment because they believed that their disease would clear up spontaneously or that at least it would not become worse.

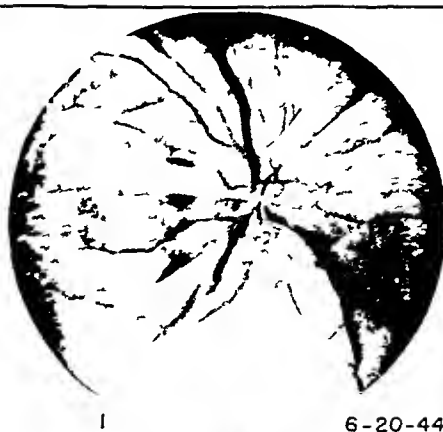
I have shown you some electrocardiograms and chest films of patients with hypertensive vascular disease who were treated with the rice diet. I will close this talk by showing you a few photographs of eyegrounds (Fig. 4). Forty-four patients with hypertensive vascular disease who had papilledema, hemorrhages or exudates, followed the rice diet for two months or longer. In all of them the retinopathy was arrested. In 20 of the 44 patients papilledema, hemorrhages, or exudates cleared up partially, in 20 completely.

# RIGHT EYE

A A H (m 47 YRS)

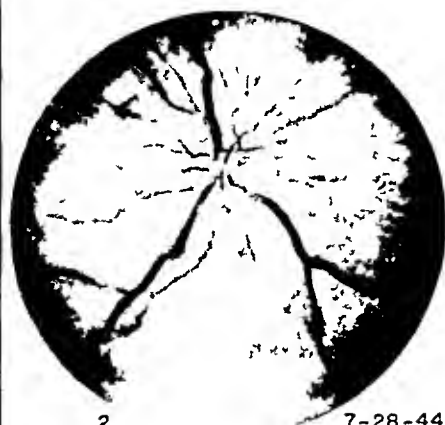
Hypertensive Vascular Disease

RICE DIET STARTED 7-4-44



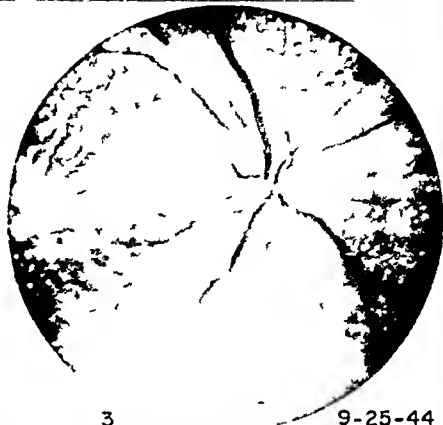
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6-20-44



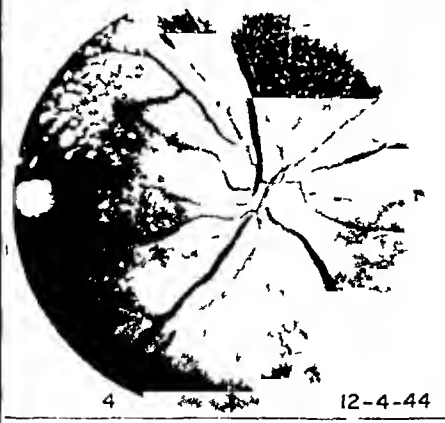
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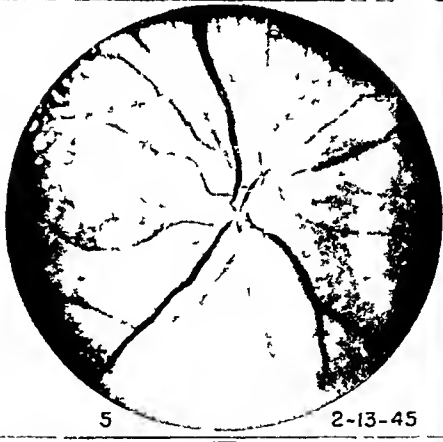
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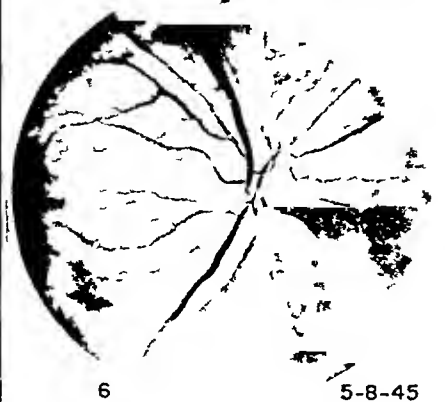
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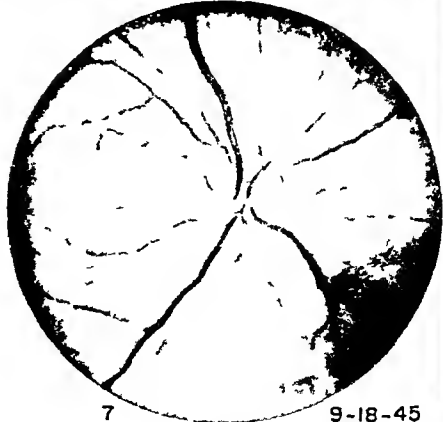
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Fig 1 A A H (m 47) Hypertensive Vascular Disease Rice diet since 7-4-44  
Right eye Disappearance of papilledema, hemorrhages, exudates

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## PATHOLOGY, OLD AND NEW\*

*Middleton Goldsmith Lecture, New York Pathological Society*

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## INTRODUCTION

NO compliment that might be paid by the New York Pathological Society could quite equal that of the invitation to deliver the Middleton Goldsmith Lecture on this occasion. No words could fully express the deep sense of gratitude I feel for the honor of making this address, a task I face with all humility. The remarks of Gregg<sup>1</sup> at another celebration apply equally well here. "Without aspersions on lesser anniversaries we may well at once declare that no celebration can equal the first centenary. You are still young enough to glory in your age, yet old enough to boast of your powers of endurance. You are so encouraged by your stout survival as even to flirt with ideas of going on forever." The congratulations and best wishes of all those interested in pathology, not only for itself but for its meaning to medicine and biology, are due this Society.

## SOCIETIES FOR PATHOLOGY

It is said that Riva, physician to the pope, founded a society for pathologic anatomy in Rome in the middle of the seventeenth century and established a museum, but the record is not altogether convincing. In keeping with the notable accomplishments of France in pathology in the first part of the last century, the Société Anatomique of Paris was established under the guidance of Dupuytren in 1803. It survived only five years, the president for the final year being Laennec. It was reconstituted in 1826 with Cruveilhier as president and is the oldest society in the world with a dominant interest in pathology. Riesman<sup>2</sup> states that a pathological society was formed in Philadelphia in 1839,

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with William Wood Gerhard as president, the purpose being the exhibition of pathologic specimens and the preservation of suitable material in a museum. It lasted only a few years and no trace can be found after 1843. It seems certain that the New York Pathological Society is the oldest in continuous existence on this continent. Being a Philadelphian, and imbued with what might be called the lococentric spirit said to characterize that region, I would have been pleased to find that it had the oldest society devoted to pathology. Such may be true in a sense, but the society was evidently a feeble infant that could not outlive childhood. Nevertheless, injured pride is somewhat mollified by Riesman when in reference to the permanent society born in 1857, he says that Samuel D. Gross, the first president, was "the first real pathologist of this country."

Horner published a text on pathology in 1827, but the book written by Gross which appeared 10 years later was the first significant treatise on the subject in this country. It must be admitted, however, that Gross was principally a distinguished clinician rather than a career man in pathology. The same can be said of all those prior to Lobstein and of many after him. Thus the societies established in the middle of the nineteenth century could not be called societies or associations of pathologists because in this country there were no pathologists in our sense of the word. Perhaps that is partly the reason for naming the society pathological. The purist groans at the adjective because of its implication of disease in the very organization. In addition, the founders had not the advantage of the style advocated by the publications of the American Medical Association, otherwise it might have been a pathologic society! It is of interest that the American Association of Pathologists and Bacteriologists was not formed until 1900, the American Society for Experimental Pathology until 1913 and the American Society of Clinical Pathologists until 1922. The Deutsche Pathologische Gesellschaft was started in 1898 and The Pathological Society of Great Britain and Ireland in 1906.

### WHAT IS PATHOLOGY?

In any discussion, it is wise to arrive at a general agreement as to terminology. In our times, it may well be said that a pathologist is a person who devotes his career to the study and practice of pathology. Dean<sup>3</sup> says the pathologist "should be able to say 'I am a pathologist,

I reckon nothing which appertains to disease is without interest to me ' To the pathologist all things, at any rate all medical things are pathology " Be that as it may, we still should try to define pathology I think we can agree that it is a subject pursued principally in the laboratory utilizing all the tools of morphology, mathematics, physics chemistry, physiology, bacteriology, immunology and the like to explain the origin, course and nature of abnormal form and function

But what about the relation to the clinic and the living patient? Is the pathologist to be a savant in the sense of Richet,<sup>4</sup> one whose only object is the discovery of the truth? Evidently there are some who think so Boycott,<sup>5</sup> for example, said at the dedication of the Pathological Institute at Montreal "The time has now arrived when pathology must recognize that it is a science which can and ought to stand on its own feet and pursue its own end, which is the study of pathology, not the study of medicine and surgery " He went on to say that there are two sorts of pathologists, those whose real heart is in the clinical application and "those who are in pathology because they had it laid upon them to try to know about the reactions of living things to injury and disease" without any particular or direct reference to human welfare Boycott lived in pathology as a science for itself and this attitude was shared in large measure by Oertel<sup>6</sup> and a few others It can be said with assurance that most of us who give our lives to pathology do so because of the crowning place it occupies in the large field of medicine

### THE THEME

The central theme of this address is the evolution of the approach to pathology as it has advanced from the deductive reasoning of the earlier workers to the more profitable inductive reasoning made possible by the expansion of information in all fields of science For the unfolding of this theme it seems profitable to undertake a cursory review of past achievements and to orientate us in relation to the time of the foundation of this Society Subsequently, morbid anatomy will be discussed, to be followed by a glimpse into the future, prophetic or not as only time will tell

### HISTORICAL PERSPECTIVE

The history of pathology has been too well presented by Long,<sup>7</sup> by Krumbhaar<sup>8</sup> and others to justify a lengthy discourse here That

would be presumptuous before this audience I should, however, draw your attention to the fact that when this Society was born, there were few professional pathologists in the world, indeed none existed in this country. The very group which organized the Society, including Middleton Goldsmith himself, were essentially clinicians who realized the importance of pathology to medical practice and consequently gave the subject intimate study. Peters<sup>9</sup> called them pathologists but they did not devote themselves principally and primarily to the subject.

A history of pathology in ancient times, the middle ages, the renaissance and well into modern times is a story not of a special field but of medicine as a whole. Long<sup>7</sup> comments on the fact that during the 5000 years of the Egyptian dynasties, there must have been at least 750,000,000 bodies prepared for burial but the descriptions are devoid of references to morbid anatomy. Yet there is little doubt that the Alexandrians performed autopsies of a sort as indicated by the description of the woodeny or stony-hard liver with ascites, credited to Erasistratus. It is a sad circumstance that the records of the Alexandrian school are only preserved second-hand in the writings of Celsus. According to Singer,<sup>10</sup> the first frank reference to a postmortem examination was made "when, during the plague of 1286, one of the bodies was opened in order to determine the nature of the disease." In my survey of the subject I found little record of autopsies until the fourteenth century, when they were performed at Salerno, Bologna and Padua.<sup>11</sup>

In the sixteenth century, progress began with the dissections and autopsies of Vesalius, Eustachius, Paré, Donatus and Schenck von Grafenburg. During this time Antonio Beniveni recorded 20 postmortems, subsequently published by his brother. More important but less widely known is the book of Jean Fernel of Amiens whose volume VII entitled *Pathologiae* was the first codification that could be called a text on pathology (Long<sup>7</sup>). Not to be forgotten is the influence exercised by the development of printing, which in all fields permitted men to exchange, pool and transmit knowledge. Without this, inductive reasoning could not have evolved. Probably of equal importance was the beginning of political liberty in the founding of the Dutch Republic, for this carried with it the initiation of freedom of thought and of scientific research.

The seventeenth century provided such men as Bartholin, Malpighi, Glisson, Sylvius and that Riva who is said to have established a society

for pathology In the latter part of that period Bonet or Bonetus published his "Sepulchretum," a landmark to be sure, excellent for its time, but now only of historic value

The eighteenth century had many notable figures but for our purposes Morgagni, whose profile graces the seal of your Society, was the greatest<sup>1</sup> His "De Sedibus," based on letters to a friend and then revised, appeared in 1761, when he was 71 years old The autopsies were not systematic in our sense, but the publication showed a keen appreciation of clinico-pathologic correlation John Hunter's protocols are more satisfactory, but still inadequate The latter part of this century is marked by the publication of Matthew Baillie's atlas and text, to my mind the first to introduce real pathology in concrete form

It was not until Rokitansky began his work that well systematized methods and protocols became prevalent When he was 58 years old he performed his thirty thousandth autopsy and Long states that by the time of his death at 68, he had available the records of 70,000 autopsies Some of you may remember Theodor, the diener at the Allgemeines Krankenhaus, who in my day said that in 10 years he had assisted at 30,000 autopsies Perhaps George Taggart in his many years of faithful service at Blockley has had as great an experience The vast material in Vienna was by no means the sole cause of Rokitansky's great contribution He was a pathologist in the truest sense, even though his deductive interpretations were faulty He brought pathology into the soul of medicine His stimulus was so great that as Roessle<sup>13</sup> remarks, a small shabby dead-house in the furthest corner of the Allgemeines, "a wretched barrack" as Kussmaul called it, became the medical center of Vienna

Our song of great men reaches a grand crescendo with mention of Virchow Inspired by Johannes Muller, he entered pathology under Froriep and in addition to becoming a prosecutor of great skill began his investigations We need not detail his work but can agree with Welch that the establishment of cellular pathology "marked the greatest advance which scientific medicine has made since the beginning"

#### CHAIRS OF PATHOLOGY

In the nineteenth century, when Bichat, Rokitansky and Virchow flourished, the first part was marked by the contributions of the French, including such men as Pinel, Corvisart, Laennec, Louis and others A

most significant item, however, was the creation of the first chair of pathology in 1819 at Strasbourg, during one of the times when it was French. This was created at the suggestion of Cuvier and occupied by Lobstein, the first chair devoted solely to pathology. Seventeen years elapsed before Dupuytren suggested the chair at Paris, which Cruveilhier occupied in 1836, and another decade passed before the establishment of the chair at Wurzburg, created for Virchow when his revolutionary ideas forced him to leave Berlin. In the meantime, Carswell occupied the chair of morbid anatomy in London in 1831 and Johannes Wagner became extraordinary professor at Vienna in 1832. Berlin awaited the return of Virchow in 1856. Chairs were established at Harvard in 1847, Pennsylvania in 1867 and at the College of Physicians and Surgeons in 1875. It was later, however, that the professors devoted their full time to the subject. But as Krumbhaar<sup>s</sup> says, before the close of the century "every self-respecting medical school had an independent chair for this important subject."

#### ORIENTATION OF FOUNDERS

If time permitted, the general cultural level of our country in the 1840's might be reviewed, but we should recall the limitation of communications, no telegraph, no telephone, dreadful roads, railroads not to be important for 20 years, ill-paved streets, poor water supplies, inadequate sewerage, not even gaslight or bath tubs. No radio, no juke-boxes, no ice cream cones, none of the accretions of our modern civilization! And yet these things were not missed by our rugged forebears.

Where did pathology stand in 1844? Bichat, Corvisart, Pinel and Laennec were dead. To be sure, Bretonneau, Louis, Broussais, Charcot, Claude Bernard and Brown-Séquard were living, but the genius of pathology was surely moving to Britain. The Hunters and Matthew Baillie had died but Carswell, Hodgson, Bright, Addison, James Paget and Hodgkin were active as was also Gull in Ireland. Only seven years had elapsed since Gerhard had distinguished typhoid from typhus largely on the basis of pathologic anatomy. Soon the mantle of our "Fach," migrating from Italy to France to England would fall on Germany.

Already Johannes Muller had as pupils Schwann, Henle and Virchow. The cell theory resulted in the publication of books on patho-

logic histology, by Vogel in 1843 and by Lebert in 1845. Johannes Wagner had died but his pupil Rokitansky was bringing out the great *Handbuch* during the forties. Virchow had been graduated in medicine just a year, but the *Archiv* known by his name began publication in 1847. Yet to develop were his pupils Cohnheim, Klebs, von Recklinghausen, Rindfleisch, Ponfick, Orth, Hoppe-Seyler, Salkowski and others. Weigert was born in 1845 and Ziegler in 1849, Schmorl in 1861, and Aschoff in 1866. In our country, Delafield, Prudden, Welch, Councilman, Mallory, Ewing, Hektoen, Flexner, Wells, Pearce and many others with names made familiar by their work had yet to appear on the horizon. Theobald Smith was not born until 1859 and his reports on cattle fever of Texas did not appear until 1890, the first convincing proof that arthropods can be vectors of disease. Pathologist, bacteriologist, parasitologist, immunologist, scholar, savant and practical scientist, kindly gentleman, he was to my mind the greatest figure American Medicine has yet produced. William Bulloch<sup>14</sup> said "It is certain that America in days to come will look at him with that veneration with which France cherishes the name of Pasteur and Germany that of Robert Koch."

#### DEDUCTIVE AND INDUCTIVE REASONING

A little later than the time of the founding of this society occurs the dividing line in pathology between deductive and inductive reasoning, the line between pathology, old and new. The investigators of the remote and even recent past were obliged to employ deductive thinking, or the analytic form of reasoning. Thus a group of symptoms and signs was correlated with anatomic observations. Our forebears had not a sufficient number of instances to set up generalities from which subsequently to synthesize their information. Nor did they have chemical, physiologic or other facts on which they could base inductive reasoning. Even up to recent times, the correlation of the clinical manifestations and morphologic demonstrations was based on deduction and seemed sufficient, those who studied medicine in the early part of the current century will recall that much of their instruction was thus founded. A concrete illustration of the defects of the method may be given by reference to the studies of Richard Bright, who observed the association of the hypertrophic heart with chronic renal disease. The one accompanied the other, but why that was true could not be ex-

plained with the information available in his day. Purely as theory he suggested the importance of peripheral resistance. The intervening phenomena were unknown to him because physiology had not explained the stimulus to hypertrophy offered by stretching of hollow muscular organs, diastolic stretching of the chambers of the heart was not in the picture. A century had elapsed since Stephen Hales had shown that there is pressure within the arteries, but another century was to elapse before readings of blood pressure were common clinical practice. Bright thought of a chemical stimulus to the heart, but even now the exact basis of hypertension is not fully clarified.

The pathologist and, as Prudden<sup>15</sup> put it in a letter to Ewing, "his satellite, the practitioner" must necessarily await the development of instruments of precision, of chemistry, physiology, and ancillary sciences in the biologic field, before inductive reasoning could be practiced. W. W. Keen<sup>16</sup> has emphasized the significance of instruments of precision in the advancement of science and human welfare. To us as pathologists, the microscope takes first place in this category. Haden<sup>17</sup> says "the name microscope was given by a physician, a physician was the first to make practical use of the microscope, three of the five great microscopists of the classical period were physicians." Nevertheless, this instrument was most widely used by laymen. More than a decade after this Society was founded, Carpenter<sup>18</sup> said in the preface of his book that the microscope served both for scientific research "and as a means of gratifying a laudable curiosity and of obtaining a healthful recreation." Roger Bacon used a simple lens and Leeuwenhoek improved it by shortening the focal length. There is general agreement that the first compound microscope was made by an optical worker, Zacharias Janssen, about 1590, at Middeburg on that island of Walcheren so recently subjected to the fury of war. This instrument enlarged objects nine diameters. Robert Hooke built a better compound microscope in 1665, but it was not until 1693 that magnifications of 100 diameters were produced by Marshall and not until 1716 that Hertel used a reflecting mirror. Schlumberger<sup>19</sup> states that in 1807 van Deyl "produced a satisfactory compound microscope with an achromatic objective and a magnification of 229" diameters. But the history of the microscope as we know it is more recent.

Policard<sup>20</sup> starts the story in about 1848 in the town of Jena, four years after your establishment in 1844. The achromatic lens had already

been produced, but the microscope was not yet sufficiently precise. Karl Zeiss was a builder of scientific apparatus, employed in the laboratory of physics at the University of Jena. He enlisted the aid of Ernst Abbe, Professor of Medicine in the University, who with help of the mathematician Magnus, planned the sub-stage condenser. Zeiss and Abbe ultimately realized the necessity for good optical glass which was finally produced by Schott. This group working through the years ultimately created the modern compound microscope, with its illumination, optical precision and resolution, about 1872. The development of the stereoscopic microscope, the binocular microscope, the ultra-microscope, the petrographic microscope and its modifications, the telemicroscope and the electron microscope naturally followed.

Provisions for sectioning and staining are even more recent. The freezing of tissues for sectioning was first practiced about the time this society was founded, but the sections were made free-hand or by the Valentin double-bladed knife. Objects were embedded in paraffin by Klebs in 1869 and in celloidin by Duval in 1879. The mechanically precise microtome was probably first used by Thoma in 1881. Although Hannover used chromic acid for fixation in 1844, yet Flemming's fluid was not announced until 1882, Zenker's fluid in 1894 and formalin in 1893. Staining by alum carmine was done by Gerlach in 1858, but alum hematoxylin was not used until 1865. Eosin was first used as a counterstain in 1875. Von Recklinghausen used silver salts, but for modern staining methods we are indebted particularly to Weigert and to Ehrlich, and in this country to Mallory. Smith<sup>21</sup> gives an excellent bibliography. The society was at least half a century old before pathologists had at hand microscopic sections thin and well stained and a satisfactory microscope with which to study them.

The use of experimental methods in the study of problems in pathology was carried on by many early investigators, notably John Hunter, but the beginning for professional pathologists was the work on migration of leukocytes reported by von Recklinghausen in 1863, to be followed by his experiments on inflammation in the cornea of the frog in 1867. More impressive and the keystone of this type of work was Cohnheim's publication on inflammation and suppuration in 1867, also in part on the frog cornea but particularly on the frog mesentery. Here for the first time were explained the phenomena of exudative inflammation. Cohnheim showed the influence of the vascular system,



"ohne Gefasse, keine Entzündung" and identified the leukocyte as the forerunner of the pus cell. This was followed by the work on thrombosis, embolism, infarction and other topics. Welch brought the inspiration of his teacher to America, where the experimental method by the end of the nineteenth century had taken root and flourished. MacCallum<sup>22</sup> wrote about his course in 1906, 1907 and 1908. This was followed by Pearce's report in 1911<sup>23</sup> and then by numerous others, including a handbook on the subject by Wagoner and Custer.<sup>24</sup> Richard Pearce said that "The great continuous advances in medicine resulted from organized laboratory effort based on the principle of exact experimental methods."

These applications of the experimental method were made increasingly useful with the strides in the latter half of the nineteenth century and subsequently, of pure science, chemistry, physiology, bacteriology, immunology, etc., including recently the study of hormones and nutrition. In the latter connection witness the investigations on tumors of endocrines and the explanation of the origin of Laennec's cirrhosis.

These various techniques, facilities and basic information were not available to the founders of this society, to their predecessors or their immediate successors. They were limited to deductive reasoning. Paraphrasing Pack and Brooks,<sup>25</sup> the morbid anatomist of the old days depended on deductive reasoning based on his extensive experience in morphology, but his successor reasons inductively because of his better basic foundation.

Note that I have avoided the terms experimental pathology, pathologic physiology, pathologic chemistry and the like. This is deliberate because I believe that these implements are readily available to the pathologist. Many of the techniques can be mastered by the educated pathologist, and in his hands become the tools of study and research. In modern institutions, collaborative research is possible when the pathologist does not or cannot acquire skill in the more complex procedures. He often needs guidance in methods and aid in interpretations, but always his studies are directed toward the understanding of disease.

No study of disease can be informative and satisfactory without incorporation of etiology. Causative factors may be predisposing and precipitating, but as Gregg<sup>1</sup> indicates a third factor is also important, namely perpetuating. The last is of especial importance in reference to chronic disease of any kind, mental or organic. It must be significant in geriatrics, a field assuming magnitude in our aging population.

The development of chemistry, physiology and experimental methods has gone along with bacteriology and immunology. Thus etiology has progressed. Pathologists can now interpose developmental mechanisms between cause and effect. This is the province of inductive reasoning, based on a premise of collected facts. Pathologists can also think in terms of causality, a broader conception than cause. For every cause there is a causal connection before the effect. Oertel,<sup>26</sup> whose philosophic comments have often failed of the recognition they deserve, says that "Roux, the founder of evolutionary mechanics, insists that every causal knowledge of a phenomenon must include a complete connected chain of events which are responsible for it." I refer to Oertel further because of the validity of his views. The series of events leading to an effect must be put in their lawful order. Every occurrence bound to a sum of circumstances necessitates the occurrence. To say that a certain bacterium causes a certain disease gives no information about the manner, sequence and mechanisms of the events, and is not satisfactory to the critical mind. He quotes Tendeloo's definition of pathology as the science "of disease producing constellations." The doctrine of causality must be utilized if etiology is to fill its place in pathology and medicine. It can furnish links in the chain of predisposing and exciting factors and particularly in reference to those perpetuating factors now in the foreground. Causality must occupy a large place in inductive reasoning.

In passing I cannot refrain from mentioning Oertel's strictures on teleology, the exact opposite of inductive reasoning and causality. The term comes from the Greek *telos*, meaning goal or purpose. "It is commonly stated that a thing happens in the human body because it serves a certain (generally beneficial) purpose, that is, the end result is taken as an explanation of the mechanism of its occurrence. A thing happens in nature, because a causal chain of preceding events necessitates it." Teleology adds nothing to precision of thought or exact inquiry, I have said. "The doctrine of purpose should not be permitted to smooth too easily the paths of learning, especially if this entail a sacrifice of the critical analysis of cause and effect." Even the teleologists are put to it to find anything beneficial in the growth of malignant tumors! Scientific progress and teleology are permanently at odds.

## PLACE OF MORBID ANATOMY

Does this discourse on deductive and inductive reasoning, the application of functional studies and the logic of causality mean the abandonment of morbid anatomy? Rous<sup>27</sup> reached the climax of assent in one of his early papers when he referred to morbid anatomy as "the dried stockfish of the subject," and his condemnation echoes that of several others. But let us look elsewhere. Boycott,<sup>7</sup> that advocate of pathology for its own sake, says that pathology began with morbid anatomy "and in this still finds its fundamental basis." Further, "the quaint notion that morbid anatomy is played out comes only from those who are ignorant of what the anatomist has to say." Turnbull<sup>28</sup> in his obituary notice of Schmorl comments that "to those who had been taught in England that morbid anatomy was a dead subject the first few days with Schmorl became an unforgettable revelation." Roessle<sup>29</sup> says that "Pathologic anatomy remains the supporting pillar of the giant growth of medicine." F. von Muller,<sup>30</sup> who did more to establish the modern clinic than any other single person with the possible exception of Osler, in his retrospect in 1937, expressed the view that Corvisart in France and Rokitsansky in Austria put pathologic anatomy in the foreground of medical thought, and thus furnished the basis for modern medicine.

Morphology does not disclose the disease as such, but as MacCallum<sup>31</sup> said, it furnishes "the changes underlying the manifestations of disease." We may go further and say that for most conditions, morphology serves better than any other method for the identification of disease. This is illustrated in the daily life of the pathologist with his autopsies and surgical specimens. All thoughtful clinicians depend in large measure on this well established fact and it is often basic to clinical research. Morphology is fundamental to research in pathology. The time has not passed, in my opinion, when it cannot add its own contributions to advance in pathology as well as the broad field of medicine. Furthermore much of research in pathology by the experimental method depends on morphologic identification of lesions produced. The newer knowledge of hepatic cirrhosis, of hypertension, of avitaminoses and other conditions depends on morphologic identification. Nowhere is this less true than in experimental investigation of neoplasms. Rous himself, in spite of his earlier scorn of pathologic anatomy, has published beautiful illustrations of the tumors he has so well studied. I am

convinced that morbid anatomy is of the utmost importance to our subject, that the tutelage of our pupils must be largely devoted to training in this field, that in itself it is a place for exercise of skill and judgment, and that no one can be called a pathologist unless he is trained, experienced and competent as a morphologist. He cannot adequately perform hospital duties, teach, or engage in research without pathologic anatomy. It is not dead, it is living, progressing and holds much for the future.

That morphology is all of pathology cannot be maintained and I agree with Symmers<sup>31</sup> who says "That individual who confines himself to the study of pathologic anatomy without attempting to bring it into harmony with the signs of altered function is blind in one eye." Even we cloistered laboratory workers realize that monocular vision is devoid of perspective, and without perspective the pathologist cannot fill his place in the cosmos. The rapid advance of pathology in recent times has been due as Klotz<sup>32</sup> says, to "utilizing the principles of chemistry, physics and biology, but wedding none of these to the exclusion of the other." I still insist that pathologic anatomy has furnished the ground work for most of the advances in medicine and pathology, continues to do so, and when properly pursued will do so in the future both for its own sake and as a foundation for functional studies.

#### FUTURE OF PATHOLOGY

And finally, what of the future? That, in my opinion, depends upon pathologists rather than pathology. The subject has become so vast that no one person can master its entire scope. Yet all can have a broad interest in the whole field and can do his share, great or small, in its progress. It is a truism to say that if it remains static, it does not only fail to advance but retrogresses. Those satisfied with the present are a hindrance to all the others.

Kracke<sup>32</sup> sets up five groups of pathologists: (1) Teachers, who may be confined in academic seclusion. (2) Hospital pathologists covering all divisions of laboratory medicine. (3) Hospital pathologists for a group of smaller hospitals. (4) Pathologists in private practice with few autopsies. (5) Governmental pathologists. He overlooks the pathologist engaged in a privately supported institute for research. I think the divisions may be simplified. There is the pathologist who because of his academic, governmental or research post has the interest,

material associations and facilities to be a productive investigator. He is comparable to the full time clinician. He must be expert in the broad field even though his research may be highly specialized, but he leads in and guides acquisition of knowledge. In contrast is the pathologist in hospital or private practice, who can be compared with the clinical practitioner, and these are on the "firing line" of medicine.

In the first group may be included the professor of pathology in the medical school and the institutional research worker. The former is in a position of serious responsibility. He represents pathology in an educational institution and its associated hospitals. To do so he must be a master of his subject, a referee in pathologic diagnosis, an inspiration to a rising generation of physicians, a scholar and investigator. The position of pathology in the curriculum, joining together the laboratory sciences and the clinics, forces him to be in the forefront of medical education, he should be an educator. This qualification has led to his appointment as dean in many instances. Parenthetically it may be said that if this duty benefits pathology, except through its supposed prestige, the advantage is not fully apparent. The professor exercises his influence not merely through medical students but also in significant degree through those graduates who are associated for a short time in preparation for a clinical career or for a longer service in training for a life work in pathology. That these ideals can be fulfilled in great measure, even in our land, is illustrated by such figures as Welch, Prudden, T. Smith, Ophuls, Councilman, Mallory, Pearce and Wells, to mention only some of those no longer living.

The pathologist in the research institute, governmental or private, is charged with much the same responsibility, save for instruction of medical students, and should possess much the same qualifications. He must be armed "with the intellectual habits and the methods of 'pure science' that he may be fit to cope later with the impurities of nature" (Rous<sup>27</sup>). In addition he must be blessed with initiative and fruitful imagination, for upon him much of the progress of pathology depends. He should leaven the whole institution, not only by his own work and his aid to other investigators, but also by that critical turn of mind which characterizes pathologists more than any other group. His addresses and publications enlighten the profession and ultimately the public. His release from routine gives him extraordinary privileges in the way of research, a greater freedom than is possessed by other pathol-

ogists His opportunities put him out in front and entail large responsibilities not only in his selected field but in pathology as a whole

The practicing pathologist in the hospital usually carries a heavy load of routine He too should be a master of his subject in order to lend his aid in diagnosis and treatment That he can possess equal facility in all divisions of pathology is not to be expected, but at least his training and experience should make him dependable in what has been called "tissue diagnosis" and competent to direct all the other activities He represents pathology in his institution and his community His laboratory should be "the axis about which the scientific work of the hospital revolves" (Simpson<sup>34</sup>) The private practitioner of pathology should be similarly motivated

The future of pathology depends in large measure upon the skill thoughtfulness and precision with which this routine worker integrates his activities with the general medical procedures of his institution and professional community In the welter of the daily job he must maintain and impart the scientific habit of thought

The future of pathology depends also on the academic pathologist The impression he creates on students, colleagues and the community, will influence the respect in which his field is held The same is true of the pathologist in the research institute That impression, to be favorable, must be based upon the solid substance of the pathologist He must be well informed, well trained, energetic, of broad vision and sympathetic Form of expression is also important, but no superficial accomplishments can replace basic realities

The future of pathology depends also on research There are those endowed with that insatiable curiosity which for its satisfaction demands investigative study Curiosity is "probably the outstanding characteristic of modern thinking" (A Flexner<sup>35</sup>) The drive for production is a corollary of curiosity, and it brooks interference only with impatience Nevertheless, circumstances often determine how far and well this inherent urge can be satisfied Obviously, opportunity is greatest in the research institute and often excellent in the university but all too frequently least in the general run of hospitals Then too the personnel differs, because appointment to these various types of position is often by natural selection But of this I am sure, that if the urge exists research will be accomplished, even though limited by burdens of routine lack of facilities and some limitation of mental endowment The hospital

pathologist may not carry on intensive continuous investigative studies but he invariably can, if he so desires, make contributions of greater or lesser importance to the sum of human knowledge. Being a fine pathologist aids in his selection of projects but at the same time adds to his responsibility to further the general lore of his subject, through dissemination of information which he collects. A good case report is not to be scorned, in itself it may have importance and when added to others may furnish a collected series of great value. We must admit, however, that a good routine job may be done without high scientific attainments.

From the viewpoint of significance, the publications of the institute or academic pathologist usually have great weight, but from the viewpoint of human welfare, the hospital pathologist can be eminently useful. To be sure there is an aristocracy of the intellect and correspondingly an aristocracy of pathologists. This is not determined by participation in societies and meetings but by attainment in scientific pursuits. It should not justify envy or awe on the part of the less fortunate nor an attitude of superiority on that of the distinguished investigator. Mutual respect founded on a clear conception of the aims of all groups, will go far in preserving and advancing pathology.

"I do not choose" to discuss economic questions. It would be stupid to ignore this matter entirely. Funds must be made available if pathology is to advance. Salaries must be sufficient for the pathologist and his family, the best work can be accomplished if personnel is reasonably free of financial worry. Money alone can provide space, equipment, materials and all the intricate facilities necessary. Young people may enter the field without foreknowledge of their future, but they do not stay unless they have reasonable assurance that if they survive competition they can face their careers with a certain degree of equanimity. Nevertheless, in my opinion, the economic aspects are largely dependent on the pathologist himself and what he can offer to science and medicine.

We have pointed out the migration of the major activity in pathology from Italy to France to England and to Germany. On what shoulders will the mantle next fall? Where will the muse bestow her blessing, her genius, her opportunities and her responsibilities? Will it move east to Russia or west to America? Prophecy is futile, but we have the example of a coincidence of decline of German pathology, in spite of Aschoff, Roessle and like spirits, and the rise of National Socialism. No

one can say with certainty whether this concurrence is due to politically instigated materialism and insistence on immediate application of science or whether it is in large part economic. In either event it is attached to loss of freedom of the investigator and teacher. Germany in the last decade and a half has lost sight of that truth so well enunciated by Abraham Flexner in his address, "The Usefulness of Useless Knowledge"<sup>35</sup>. Applied science, whether in medicine or other fields must have its backlog of pure science, truth for its own sake. Only freedom of research can furnish this fund of basic information and only freedom can guarantee its wisest and most fruitful application. If Russia were to grant such freedom, she might well inherit the mantle, or at least part of it. We must see to it that the muse which has shown us her favor in the last half century does not pass us by. She will only grant us her further benefactions provided her devotees are not shackled.

#### EPILOGUE

Your kindness and patience have allowed me to review the background of pathology, to orientate the time of the establishment of the New York Pathological Society in the history of our field and to point out that the evolution of science in general has permitted the change from deductive to inductive reasoning, the milestone that divides the old pathology from the new.

I hope you share my conviction that pathology has great promise, but that fulfillment and performance depend on the pathologists themselves, their quality more than their numbers, their inherent merits, their ability and their rigid integrity. With Link,<sup>36</sup> we can wisely advise "the struggle for improvement rather than the guarantee of perfection, the adventure of achievement rather than the certainty of success." It is for us and our successors to guard the tower and keep the faith, a task in which this distinguished Society, according to its history and tradition, will share in full measure.

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MAHLON ASHFORD, *Editor*

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BULLETIN OF  
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AUGUST 1946

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MEDICAL MANAGEMENT OF  
PERIPHERAL VASCULAR DISORDERS\*

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THE four chief conditions in the field of peripheral vascular disease which require the attention of the general practitioner of medicine are arterial embolism, phlebitis, arteriosclerotic disease of the arteries of the extremities, and thrombo-angitis obliterans. I shall discuss briefly some important considerations in regard to these four conditions.

Most physicians are familiar with the fact that emboli to the extremities generally arise from diseased hearts, but apparently few of them keep this knowledge in mind when handling cardiac cases. This may explain their frequent failure to recognize promptly the occurrence of an embolism to a major peripheral artery. This complication should be anticipated in every case of acute coronary thrombosis and chronic rheumatic or arteriosclerotic heart disease and particularly in those patients in whom the hearts are fibrillating. The physician confronted with a case of heart disease of this type should at once make sure that the normal pulsations in the hands and feet are palpable and should make a record of any pulsations which are absent. Any complaint of sudden

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\* A Friday Afternoon Lecture given at The New York Academy of Medicine January 2, 1946.

numbness, coldness or pain in an extremity should at once arouse his suspicion that an embolism to a major artery has taken place. If this suspicion is confirmed by objective signs, such as loss of pulsation in the vessels, pallor and coldness of the extremity, anesthesia of the foot and muscular paralysis, he should recognize immediately that an emergency has arisen which needs prompt action on his part. It has been my observation that many times precious hours are lost when an embolism occurs, and it is not until gangrene is already beginning to develop that the family physician recognizes that a catastrophe has taken place.

An example of such delay is the following. Some months ago I was asked to see a patient by an experienced specialist in internal medicine. Two weeks previously this patient had had a severe acute coronary thrombosis following which he was desperately ill. Five days before I saw him he complained of numbness in the left foot, but because of the concentration of the physician and nurses on the cardiac problem, little attention was paid to *this* complaint. The numbness persisted and the following day the nurse noted that the foot was cold. After two more days bluish discoloration of the great toe was noted, and this development induced the attending physician to call in a specialist in peripheral vascular disease because he thought there had been a thrombosis of the dorsalis pedis artery. Up to this time no treatment had been directed toward the lower extremity. Because of the use of sedatives for the cardiac condition the patient had not complained of pain in the leg. Examination showed the left lower extremity cold and cyanotic from the knee down. There was beginning discoloration of the great toe. There was complete paralysis of the leg muscles and complete anesthesia below the middle of the leg. The femoral pulse was present but the popliteal pulse was absent and there was no pulsation in the foot. Obviously, an embolism had lodged at the bifurcation of the common femoral artery, the most favorable location for surgical removal. After five days of delay, necrosis of the tissues was already proceeding rapidly, and it was too late to accomplish anything by medical or surgical therapy. A mid-thigh amputation was the only possible treatment, and in this patient's precarious condition, it carried a great hazard.

Your opportunity to be of greatest help to your patient is lost unless an embolism is recognized immediately after it occurs. Prompt action

should follow, and certain steps should be taken in an effort to prevent gangrene from developing

The two most common mistakes made in the treatment of embolism are elevation of the extremity and the application of heat. Three out of every five cases of arterial embolism seen in consultation have been treated in this manner. Reflect a moment on the effect of these procedures. An extremity which suffered an embolism has been deprived of most of its blood supply. Is that blood supply increased or restored by elevating the leg? The blood pressure in the extremity distal to the point of occlusion is sharply reduced, and is scarcely adequate to force the blood to the toes. When the extremity is raised, the blood must in addition be pushed up hill. Obviously, elevation of the extremity still further impairs circulation and is harmful. The proper position for an extremity suddenly deprived of its blood supply is sloping downward. When the leg is dependent, the arterial circulation is aided by the action of gravity. The head of the bed should be raised on chairs or blocks so that the level of the feet is below that of the hips. Since the circulation is most precarious in the toes, it is an additional safeguard to turn the patient occasionally so that he lies face down with the feet extending over the end of the bed. In this position the tips of the toes are most dependent.

The second common mistake is the application of heat. The effect of warming tissues is to increase the metabolic rate and to increase the need for oxygen. When the blood supply has been suddenly cut off, these needs cannot be met, and only harm and increased pain result from heating. In many instances gangrene of the foot is due more to the improper use of heat than to the impairment of the circulation. Tissues deprived of nutrition will die, and measures are required to keep these tissues alive until circulation can be restored. It is commonplace knowledge that to preserve meat, we place it in a refrigerator, not in an oven. If we wish to preserve the tissues of an extremity until circulation has a chance to come back, we must apply cold, not heat. The simplest method is to surround the leg with covered ice bags from the toes to the knee or higher if necessary. The beneficial effect of this procedure is at once apparent in the prompt relief of pain. As circulation begins to return, the use of ice bags may gradually be discontinued.

When a major artery is suddenly blocked by an embolism, there is a marked associated spasm of all collateral arteries. Measures to relieve

this spasm are necessary to permit all available blood supply to reach the extremity. The most effective medical means of accomplishing this is by repeated intravenous injections of papaverine. The dosage used is one grain every two hours for four doses, and then every four hours until the circulation appears to be returning safely. Ampules of papaverine should be in every physician's emergency bag ready for immediate use.

Thus, the three measures which should be promptly instituted in every case of embolism are elevation of the head of the bed, the application of cold to the involved extremity, and the intravenous injection of papaverine.

A second method of relieving arterial spasm is by temporary block of the sympathetic nervous system. This can be accomplished by spinal anesthesia, paravertebral block with novocaine, or by continuous sacral anesthesia. Spinal or paravertebral block has the disadvantage that the effect wears off in less than an hour. Continuous sacral anesthesia is a better choice and is destined to be more widely used in the treatment of acute embolic episodes of the legs. If an anesthesiologist and facilities are available this form of treatment should be started immediately.

The surgical removal of an embolism should be considered in every case. Conservative treatment for a few hours is justifiable, but during this interval surgical consultation and preparation for removal to a hospital should be carried out. Best results are obtained if embolectomy is undertaken early, which means within 12 hours after the embolism has occurred. In previous years embolectomy frequently failed because of the formation of a secondary thrombus at the site of operation on the vessel. Much more satisfactory results have been obtained since the use of anticoagulants to prevent such thrombus formation. The intravenous administration of heparin is started before operation and is continued for 48 hours. Dicumarol by mouth is started at the same time, and after 2 days the anticoagulant action of this drug is sufficient to prevent thrombosis and the heparin is discontinued. Operation can be done under local anesthesia and is not a shocking procedure. In recent years reports of successful embolectomies are becoming more frequent.

Embolism to an extremity is a greater emergency than acute appendicitis. The preservation of an extremity and the saving of the individual's life are at stake. Many of these patients succumb to an amputation of a gangrenous leg. Prompt and effective team work is

necessary to save them. Each hospital should have an embolism team consisting of physician, hematologist, anesthetist and surgeon ready to act as a group whenever this type of emergency arises.

If gangrene develops in spite of all measures taken, and an amputation becomes unavoidable, operation should be delayed as long as possible. The purpose of this delay is to allow heart function to improve and to gain time for the development of collateral circulation at the site of amputation. Since most emboli to the lower extremities stop at the bifurcations of the iliac or femoral arteries, the circulation of the thigh is impaired. Amputation is usually done through the mid-thigh region because gangrene of the leg frequently extends almost to the knee. Each day gained allows a better collateral circulation to develop in the thigh. Throughout this period the discolored portion of the extremity should be kept cold, in order to relieve pain and delay the necrotic process. The patient must be watched carefully, and signs of toxemia, such as elevation of pulse and temperature, mental confusion, attempts to get out of bed, and incontinence, should be regarded as indications for proceeding with amputation.

\* \* \* \* \*

The treatment of phlebitis is the second topic of this talk. Superficial phlebitis is a benign and relatively simple condition to treat. Inflammation of the superficial veins of the legs is most frequent as a complication of varicose veins, but also occurs as migrating and traumatic phlebitis. The danger of pulmonary embolism is remote as long as the patient with superficial phlebitis is reasonably active. The most common error in treatment is to keep such a patient in bed for weeks. Bed-rest is only necessary for relief of pain, and seldom is required for more than 24 hours. Warm, moist compresses during this period are helpful. As soon as possible the patient should be taught to apply an elastic bandage and should be encouraged to walk and return to normal occupation.

Phlebitis of the deep veins of the lower extremities, on the other hand, is a serious and dangerous condition, often resulting in pulmonary embolism and death, or leaving the patient permanently disabled by a swollen and unsightly leg. It is a frequent complication of operation, confinement, or illness, and should be guarded against whenever a patient is put to bed for several days for any condition. When bed-rest

becomes necessary it is the duty of every physician to make sure that several times each day the legs are uncovered and exercised for several minutes. Flexion and extension of the knees and ankles, movement of the toes, and bicycle exercises will aid circulation in the deep veins of the legs, and prevent a thrombotic process from starting in these veins. The development of a phlebitis in the deep veins of a lower extremity usually can be prevented by proper care.

In recent years it has been generally recognized that the most dangerous period of phlebitis is at the onset, when loose thrombi begin to form in the deep veins of the calf. It is during this time, when there is no swelling and physical signs are minimal, that there is the gravest danger of fatal pulmonary embolism. Complaints of pain in the legs, vague feeling of apprehension, elevation of pulse rate or temperature, tenderness of the calf muscles, pain in the calf on dorsal flexion of the foot, all should be regarded with suspicion as indicating the onset of deep phlebitis. Allen of Boston stresses that a slight simultaneous rise in temperature, pulse and respiratory rate in a previously level clinical chart is strongly suspicious of a pulmonary infarct, and should at once direct attention to a possible phlebitis in the legs.

Several American surgeons now advocate immediate ligation and division of the superficial or common femoral vein as soon as there is any suspicion of thrombosis or phlebitis in the calf veins. Credit for this bold attack on the problem goes to Dr. John Homans, and it has been carried out in hundreds of cases in the Massachusetts General and Boston Beth Israel Hospitals. Dr. Allen at the former institution insists that ligation should be done only of the superficial femoral, while Dr. Fine at the latter hospital prefers to ligate the common femoral or iliac vessels. In several cases the vena cava has been ligated. All of the Boston surgeons agree that ligation should be done in both legs, even though there is suspicion of thrombosis in only one. This is done to forestall embolism from possible thrombosis in the second leg. At the Massachusetts General Hospital prophylactic bilateral femoral vein ligations are being done on all patients over 65 who are to undergo major surgery even though there is no thrombosis or phlebitis in the legs. It is stated that femoral vein ligation results in very little, if any, persistent swelling of the legs.

Experience has shown that even bilateral femoral vein ligation is not an absolute safeguard against pulmonary embolism, for in several

cases fatal or non-fatal emboli occurred in spite of this procedure. Such emboli arise from pelvic or other veins, or from the right side of the heart. Furthermore, the statement that little, if any, persistent edema results from this operation should be accepted with reserve. To cite a single example, I recently saw in my office an unhappy young woman of 27, who gave me the following history. Last July she gave birth to her first child. Her obstetrician said nothing to her about the importance of exercising her legs during the postpartum period. Nine days later she developed severe pain in the chest and a diagnosis of pulmonary embolism secondary to phlebitis was made. Immediately, a bilateral femoral vein ligation was done. She remained in the hospital for a month with her legs constantly elevated. Ever since there had been marked swelling of both legs, which increased during the day to such an extent that her legs bulged over her shoes. She complained of constant dragging pain in the legs and fatigue due to the weight. Examination disclosed a physically perfect body except for the legs. Both lower extremities were enormously swollen, one more than the other. The measurements of the calves were 44 cm on one side, 40 cm on the other. The average normal measurement of the calf in a female patient of her size would be 34 cm, so that in this patient there was 10 cm, or 4 inches of swelling on the worse side, and 6 cm, or 2½ inches on the other side. These measurements were made in the morning, at a time when the swelling would be reduced by rest during the night. Similarly, her ankles measured 31 cm and 26 cm. Normal average readings would be 23 cm. Thus, the worse ankle was 8 cm, or over 3 inches too large, while the better ankle was 3 cm, or over 1 inch swollen. The extremities were so unsightly and conspicuous that she is condemned to the indefinite use of slacks to conceal them. Perhaps this could have been avoided by the simple precaution of regular postpartum exercise of the legs. In any case it was an example of massive edema of both legs following femoral vein ligation, a condition which the proponents of this operation claim does not occur.

Opposed to the use of vein-ligation in thrombosis and phlebitis of the calf veins are those who advocate the use of anticoagulants, heparin and dicumarol. Many hundreds of cases have now been treated with anticoagulants, particularly at the Mayo Clinic, and numerous favorable reports are being published. For example, Barker and his associates of the Mayo Clinic report a series of 1000 surgical cases treated with



dicumarol These cases were specially selected because they had already had thrombosis or embolism, or were to undergo operations in which this complication was prone to develop Included were 180 patients who had had a non-fatal pulmonary embolism In the entire series of 1000 patients only one fatal pulmonary embolism occurred Such figures cannot fail to be impressive

The great advantage of the anticoagulant method is that thrombosis and phlebitis are controlled in all parts of the body and not just in the legs Additional operations are avoided and the inevitable tendency to swelling of the legs from the thrombophlebitis is not aggravated by further surgical ligations The dangers of this method of treatment are from bleeding, in wounds, in ulcerative lesions of the gastrointestinal tract or by hemorrhage into vital organs In the report from the Mayo Clinic previously cited, there were 25 instances of major bleeding and 39 of minor bleeding For the present no one should undertake to give dicumarol to a patient without the constant help and advice of a competent hematologist, who can make the necessary prothrombin time tests and who is aware of the contraindications to its use If dangerous bleeding should occur he will be prepared to treat the patient promptly with transfusions of fresh whole blood or by injections of vitamin K

European physicians have long been using another conservative method in treating thrombosis and phlebitis in the calf veins and this is the application of elastic bandages from the toes to the hips while the patient is in bed The effect of binding the legs snugly is to compress the deep veins, thereby fixing any thrombus and preventing its free movement This method may be combined with the use of anticoagulants

It is generally agreed that when obvious swelling of the extremity develops the danger of pulmonary embolism is greatly diminished, and ligation of the femoral vein is no longer recommended The purpose of treatment in this stage is to relieve pain and reduce swelling Elevation of the extremity and the application of warm moist compresses or dry heat have been the standard methods of treatment These are logical and correct forms of therapy Elevation of the leg helps to reduce venous stasis and swelling, and the application of heat tends to overcome any associated arterial spasm Guarded exercise of the affected leg is desirable, as this is a form of physiological massage which tends to reduce swelling It is particularly important to exercise the unaffected

leg regularly, to forestall any tendency to thrombosis and phlebitis in this leg. It is a mistake to keep patients in bed too long. As soon as pain has subsided and the temperature has become normal, an elastic bandage should be applied to the affected leg and the patient should gradually be made ambulatory. A normal sedimentation time is additional evidence that the active inflammatory process has terminated. Bed-rest beyond this point has the disadvantage that it favors development of phlebitis in the other leg.

Repeated paravertebral injections of novocaine to block the sympathetic nerves have been recommended as a form of treatment during this stage of phlebitis. It is claimed that more rapid fall of temperature, relief of pain, and reduction in swelling results from this form of treatment. The technique is relatively simple and the injections can be given at home by anesthetists familiar with the method. Unless there is some contraindication, this form of therapy is worth a trial.

Anticoagulants may properly be used in this stage of phlebitis, both to limit the thrombosis in the affected leg, and to prevent extension of the process to the other leg. I am deliberately avoiding discussion of dosage and method of administration of dicumarol lest you be tempted to use it without proper safeguards. The hematologist will know its dangers, and without his help it would be hazardous to use it.

The discussion of phlebitis thus far has been concerned with treatment of the acute phase. There remains to be considered the proper care of the later stage, which might be regarded as chronic phlebitis, but which should rather be thought of as the sequela of acute phlebitis of the deep veins. Such patients come to the physician for relief of the discomfort of a heavy, swollen, unsightly extremity. The essential cause of the persistent disability is the residual venous stasis which results from partial obliteration of the deep venous circulation. This group of patients is important from a medico-legal standpoint. Many workmen operated upon for injuries occurring during employment develop a postoperative thrombophlebitis. Not only are they disabled by the pain and feeling of fatigue in the swollen leg, but frequently recurring phlebotic ulcers require hospitalization and prolonged medical care. Such patients are a plague to insurance carriers, who must frequently pay unemployment compensation and medical bills for several years.

Treatment must be directed toward diminishing venous stasis. The three available methods are elevation of the extremity, muscular activity

and external support. Patients who suffer from this condition should be instructed to sleep with the leg elevated, and to elevate the extremity at least to the horizontal for several periods during the day. The most effective method of keeping the leg elevated during the night is to raise the foot of the bed. During the day female patients can usually arrange household work to allow several periods of rest during which elevation of the leg can be carried out. Standing for long periods in one position or sitting with the leg dependent adds to venous stasis and should be avoided.

However, all forms of activity which cause active contractions of the muscles of the legs are beneficial and should be encouraged. Contraction of muscle has the same effect as squeezing a sponge. Local venous pressure is raised and venous return flow is accelerated. The beneficial effects are quickly noted by the patient, pain is relieved and swelling tends to be reduced. Walking, dancing, swimming, riding bicycle, playing tennis, basketball and other active games should all be encouraged. It is a common mistake for physicians to prescribe rest.

The use of elastic support, either in the form of a fitted stocking, or properly applied elastic bandage is the third of the three measures useful in this condition. Such a support acts as a resistance against which the actively contracting muscles exert pressure. The effect of the combined action is to force the venous blood out of the leg. Under the stimulus of such action, collateral venous channels develop in the deeper structures of the extremity, and a more competent venous circulation is restored.

The physician is often confronted with complications which result from the patient's failure to carry out the simple measures outlined. Such complications are dermatitis, chronic cellulitis, and ulceration of the legs. It is a frequent experience to find that patients with such lesions are treated for weeks and months without success. Various types of lotions, ointments, dyes and drugs are applied, and all types of elastic, semi-elastic and rigid bandages are employed. The quickest way to clear up such a complication is to put the patient to bed with the leg elevated. The simplest type of dressing, such as warm, moist compresses followed later by bland ointments are applied. It is seldom that more than three to four weeks are necessary to heal any such superficial lesions. Ambulatory treatment of such cases should be avoided. It is expensive, time consuming, and frequently futile, and the chief result is damage to the physician's reputation.

Turning now to our third topic, the management of patients with arteriosclerotic peripheral vascular disease, we face the largest problem in this field. The many causes of arteriosclerosis, age, diet, hypertension, diabetes, gout, endogenous and exogenous poisons, are causing a constant increase in cases of this type. Most patients come to the physician because of increasing limitation in the ability to walk, but many seek aid because of rest-pain, ulceration or gangrene of the toes or feet.

The simplest type of case is the patient whose only complaint is that he must stop every block or two because of recurring pain in the calf or foot. Such a patient presents a general and a local problem. The symptoms in his leg are due to arteriosclerosis which is part of a generalized disease. What factors are responsible for the arteriosclerosis and what can be done about it? A careful history and complete physical examination may reveal an unsuspected hypertension or sugar in the urine due to uncontrolled diabetes. Tophi in the ear lobes may point to gout. Xanthomatous skin lesions will suggest a high cholesterol in the blood. A history of syphilis may be obtained. The patient may be forty or fifty pounds too heavy, revealing lack of judgment or understanding about eating habits. The careful physician will follow through any clues obtained as to the cause of the premature arteriosclerosis, and will supplement his physical examination with appropriate laboratory studies. He will then be in a position to advise his patient in regard to diet, change in living habits, and specific care of recognized illnesses, all of which are part of the intelligent treatment of his case.

The local problem is relief of the pain in the legs which occurs on walking. This can be solved only by measures which increase the circulation in the extremities. Patients who use tobacco must be convinced that it is necessary to give up this habit completely. Wide experience in the treatment of individuals with arteriosclerotic peripheral vascular disease has demonstrated that smoking aggravates this condition, and that cessation of smoking results in clinical improvement.

The most common error made by physicians in treating patients with this type of peripheral vascular disease is to advise them to spare their legs and walk as little as possible. Physiologists are all agreed that the active use of a muscle results in increase of its blood supply. The end products of cellular activity such as lactic acid and histamine are powerful vasodilators, and their local effect is to increase circulation. Therefore, it may be said that by activity the patient manufactures in

his muscles the most potent medicine which can help his circulation. It is my custom to recommend graded activity of many kinds to patients with intermittent claudication. They are particularly encouraged to walk at a leisurely pace from one to three miles daily, stopping whenever necessary for a few minutes to relieve pain. Walking is advised to and from work, and on every occasion when it is necessary to go from one place to another. Such activities as dancing, playing golf and riding a bicycle within reasonable limits are approved. It is a common experience to have patients report that as they continue to walk they are able to go further and further distances without pain. Considerable time may be required to carry out such activity but the persistent patient will be rewarded by steady improvement in walking.

The use of heat has an important place in the treatment of arteriosclerotic peripheral vascular disease. General heating of the body causes the peripheral blood vessels to dilate, bringing more blood to the extremities. The local effect of heat is to increase the metabolic activity of the cells resulting in increased production of lactic acid and histamine. These are active vasodilators which aid in increasing local circulation. Thus, both general and local heating have value.

The simplest, safest and cheapest form of heat therapy is the warm tub bath. It combines the benefits of both general and local heating. Patients should be instructed to take tub baths at body temperature for one-half to one hour once or twice daily. A pound of epsom or sea salt should be added to each bath as this tends to lessen skin irritation.

Dry heat applied with a baking apparatus or by diathermy is also valuable, but care must be used to avoid over heating. When tissues poorly supplied with blood are heated to over 100° F burns frequently result. Furthermore, heat is effective in direct relation to the period used. A temperature between 90° and 95° F maintained for several hours is an effective and safe form of treatment. Such treatment is best given during the night when the patient is normally inactive. For this purpose a specially constructed heater regulated by a thermostat is employed. Such apparatuses are relatively inexpensive and are available. Sleeping under such a heater gives the patient an effective eight hour heat treatment every night.

The value of drugs in the treatment of arteriosclerotic peripheral vascular disease has not been established. As in the treatment of coronary sclerosis, the use of theobromine or aminophyllin combined with

phenobarbital is recommended, although evidence that benefit results is difficult to establish. Potassium iodide is given in combination with these, and all three drugs are best prescribed in enteric-coated pills or capsules. Individual tolerance varies a good deal and the dosage must be adjusted to each patient.

Injections of various expensive biological products such as pancreatic extract (depropanex), testosterone, and tetrathione are highly recommended by their manufacturers, but there is little scientific evidence to support their claims. For the patient whose only complaint is intermittent claudication, their use will be disappointing. The same can be said about the use of the expensive suction-pressure glass boot and the other types of apparatus which employ the same principles.

It is important that the general practitioner should take an optimistic attitude toward the possibilities of improvement in patients with arteriosclerotic peripheral vascular disease, and he will find that his optimism is justified. Much harm is done to the morale of patients by professional pessimism. In the treatment of patients with peripheral vascular disease, just as in those with acute illnesses like pneumonia and typhoid fever, it is well to remember that nature is on the side of the doctor, and considerable spontaneous improvement may take place. Collateral circulation gradually develops to take the place of occluded vessels in many patients. When, in addition, the few simple methods outlined are faithfully carried out, improvement will result in a surprisingly large number of cases.

It is useful to point out briefly the value of hypertension in patients with peripheral vascular disease. In general, it may be stated that high blood pressure tends to protect such patients from serious complications. When sudden occlusion of a major extremity artery occurs due to thrombosis or embolism, gangrene is less likely to take place when the blood pressure is elevated than when it is low. I have frequently observed that in patients with peripheral vascular disease the circulation in the legs tends to improve if hypertension develops. On the contrary, when patients with impaired circulation in the legs and long standing high blood pressure suffer a coronary thrombosis, the associated fall in pressure may precipitate gangrene of the foot.

When arteriosclerotic peripheral vascular disease reaches the stage of ulceration or gangrene, the problem becomes much more difficult. Pain is present not only during activity, but also at rest and may be

severe. The local destructive process may be progressive and the loss of the extremity is frequently threatened. The serious nature of the lesion must be recognized, and the patient should be confined to bed. When necessary, crutches should be used to avoid weight bearing on the affected foot. The head of the bed should be elevated to aid the flow of blood into the lower extremities. Pain must be relieved by medication, and aspirin, codeine, and morphine may be necessary. Sometimes small intravenous injections of typhoid vaccine to produce slight febrile reactions may be used to relieve pain. The local use of heat frequently aggravates pain, and it should then be discontinued. Instead, local cooling with covered ice bags may give relief. Occasionally, methods to produce venous stasis, such as ligation of the femoral vein or the application of an intermittent venous occlusion apparatus has value in aiding the healing of ulceration.

The diabetic patient with advanced arteriosclerotic peripheral vascular disease presents a special problem because of his susceptibility to infection. In such patients gangrene may develop and involve only a portion of one toe. If such a limited area of gangrene can be kept free from infection, spontaneous demarcation and separation of the necrotic tissue may take place, and loss of the extremity may be prevented. However, unless meticulous attention to detail is observed, infection readily takes place at the junction of living and necrotic tissues, and quickly travels along tendon sheaths or lymphatic channels. Immediately, what appeared to be a minor trouble, suddenly threatens the loss of the patient's leg and may cost him his life. Particularly in the patient with diabetes, any local ulcerative or gangrenous lesion should be treated seriously. Weight bearing must be strictly forbidden, smoking must be stopped, the diabetes must be carefully controlled so that there is no glycosuria, the local lesion must be carefully sterilized and covered with an adequate sterile dressing, and measures to improve the circulation must be instituted. In addition, penicillin should be used locally and given by injection as a safeguard against spreading infection. If for any reason penicillin cannot be used sulfadiazene should be given in adequate dosage.

If conservative treatment results in evidence of improvement it should be continued, but failure of improvement to take place after several months should be bravely recognized by both physician and patient. There is no greater mistake than to continue futile conservative

treatment in a patient with spreading gangrene until his general condition deteriorates to the point where he cannot survive an amputation. Yet such tragic mistakes in judgment are frequently seen. While the loss of an extremity cannot be regarded lightly, it is still possible for a patient to adjust himself to it and lead a comfortable and fairly active life.

When amputation becomes necessary the level of operation requires serious thought. In most cases local operations to remove one or more toes, or a portion of the foot, will fail. Usually, gangrene of the operative wound promptly develops and spreads, and a higher amputation becomes necessary. Most surgeons recommend amputation through the lower part of the thigh. Satisfactory healing at this level can always be anticipated, but the loss of the knee joint adds greatly to the patient's disability. In most instances amputation can be performed through the middle of the leg, saving the knee joint and about six inches of the leg. A guillotine type of operation leaving the wound wide open for drainage is usually employed. An artificial leg can be fitted to such a stump and the patient can then walk very well steadied by the use of his own knee joint. The operative mortality is much lower when amputations are done through the leg instead of the thigh, and the resulting stump is seldom painful. Recently, the published figures of many of the large hospitals of New York, Philadelphia and Boston, reporting the mortality after thigh amputations were summarized. Of 637 diabetic patients subjected to mid-thigh amputation, 300 died, a mortality of 47 per cent. In contrast, in 110 unselected diabetic patients treated by mid-leg amputation by myself or under my direction, there have been only 8 deaths, a mortality of 7 per cent. In view of the many advantages I have been recommending mid-leg amputations in nearly all cases for several years.

\* \* \* \* \*

The final subject of this talk is the treatment of thrombo-angitis obliterans. The first symptom of this condition may be an attack of superficial phlebitis, or pain in a toe which is mistakenly attributed to an ingrown toe nail, or pain in the calf muscles on walking a few blocks. With progression, these symptoms become intensified, and later ulceration or gangrene of the toes may develop. Finally, the spread of gangrene and persistent pain may lead to amputation of the leg. This curious disease has been steadily increasing in frequency during the past fifty



years, and cases may be encountered in any general practice. It is a condition which occurs in young individuals, chiefly between twenty and forty years of age. Ninety-nine per cent of the patients are male, but typical examples are occasionally seen in females. All nationalities and races are affected. The use of tobacco by individuals susceptible to this substance causes the disease.

A patient with thrombo-angitis obliterans must be persuaded to give up smoking completely and permanently. It is useless to treat him unless he cooperates wholeheartedly in this respect. Many patients continue to smoke in spite of repeated warnings that it will result in the loss of a leg. In part, this is due to unwillingness to believe that they have a special susceptibility to tobacco which most people do not share. In part, it is due to the attitude of physicians who disparage the advice of experts in this field and suggest that it will be sufficient to *reduce* the amount of smoking. When gangrene finally develops it is frequently too late to prevent loss of the extremity. The most important part of the treatment in an individual who has thrombo-angitis obliterans is to make certain that he has absolutely stopped smoking.

Since most patients with this disease are young, considerable spontaneous improvement in circulation often results when the etiologic factor is removed. To speed up the return of circulation, many methods of treatment are available and some of them were outlined in discussing the treatment of arteriosclerotic peripheral vascular disease. However the most effective treatment is the repeated intravenous injection of hypertonic salt solution. The technique of saline injections is as follows. The solution used is 5 per cent sodium chloride. It is prepared in freshly distilled water, filtered, and immediately sterilized. Since bacteria grow rapidly in distilled water, immediate sterilization is important to avoid contamination. If injections are followed by chills or temperature reaction, the cause is almost always found in failure to follow this rule. Injections are given by the gravity method into a superficial vein at the elbow. Occasionally, when the arm veins are very small, the external jugular vein is employed. The initial dose is 150 cc and all subsequent injections are 300 cc. The fluid is allowed to run in fairly quickly, only about ten minutes being required for the injection. During this time patients are kept lying flat. While the treatments are being given, patients become very thirsty and many of them experience a sensation of warmth. They are allowed to get up as soon as the injections are fin-

ished and may return to work. One of the great advantages of this method of treatment is that it is ambulatory and it does not interfere with employment. The injections are at first given on alternate days three times a week, later twice a week, and the length of intervals is further increased as the patients improve. The total duration of treatment varies from six weeks to two years, depending upon the severity of the individual case. Patients are discharged when all symptoms have disappeared or when the maximum possible improvement has been obtained.

Patients with ulceration or gangrene require bed rest, and in such cases pain may be severe. If codeine or small doses of morphine fail to relieve pain, repeated intravenous injections of typhoid vaccine sufficient to produce mild fever may be more effective. Care should be used to avoid temperatures higher than 101 degrees, as excessive fever may induce further thrombosis. Occasionally, severe and persistent pain requires more energetic treatment, and in such cases exposure and section of the sensory nerves of the foot is immediately and completely effective. The nerves to the foot can be exposed by short vertical incisions just above the ankle. The nerves are sectioned and immediately sutured. By this means complete anesthesia of ulcerated areas can be produced, and such anesthesia will last for six months to a year. During this period the ulcers can be cleaned and dressed without pain, and they will usually be healed before sensation returns. By dividing the nerves low down in the leg, fibers going to the calf muscles are spared, and there is no interference with muscular activity and walking. Trophic changes in the foot do not occur, and healing of ulcerations appears to be accelerated. This operation should not be undertaken until other methods have been tried without success. Operations done in tissues with poor blood supply may result in poor healing and further complications.

More than 900 patients have now been treated during the past twenty-three years by intravenous injections of 5 per cent saline solution. Of this number over 800 have improved under treatment, and in the great majority of them treatment is no longer necessary. A careful follow-up record has been kept. Most of them are known to be in good health and are working at various occupations. No patient restored to good condition has ever had recurrence of trouble or required amputation unless he resumed smoking. In the entire group of 910 patients only sixty amputations have been necessary, 6.6 per cent. These were re-

quired only in those patients who were first seen at a stage when extensive ulceration or massive gangrene was already present, or in those who could not be induced to refrain permanently from smoking. If thrombo-angitis obliterans were always recognized and treated in its early stages, and if patients cooperated by ceasing the use of tobacco when instructed to do so, amputations for this disease could be absolutely eliminated.

When conservative methods fail and amputation is required the knee joint should always be saved. Since most patients with thrombo-angitis obliterans are young men who must continue to earn a livelihood, it is particularly important to reduce disability. With an amputation below the knee, a young man can soon walk on an artificial leg without a perceptible limp, and he has no difficulty in finding employment. Amputation above the knee is seldom justified in a patient with this disease.

Many other problems in peripheral vascular disease have not been discussed. These include varicose veins, Raynaud's disease, other types of vasomotor disturbances, and various forms of lymphedema. I have concentrated on the four most common conditions to lessen confusion and to leave with you a few clear principles of treatment.

# DISORDERS OF THE SPLEEN WITH SPECIAL REFERENCE TO THOSE AMENABLE TO SURGICAL THERAPY\*

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FROM earliest recorded times the role of the spleen in health and disease has been the subject of much speculation and controversy. Notwithstanding the fact that the past thirty years have seen noteworthy advances in our knowledge of this viscus, it can safely be said that it continues to be one of the least understood organs in the body.

In view of these circumstances, it seems fitting to review briefly some of the accepted facts about the spleen which are pertinent to any discussion of its disorders. With this in mind, its structure will be taken up first and subsequently its function.

*Structure* The human spleen is an encapsulated, fibrocellular organ, measuring on an average 12.5 cm in its greatest diameter and having the shape of a flattened tetrahedron. Grossly and microscopically its parenchyma suggests a sponge. This similarity becomes even more apparent when the fluctuations in its size and the obvious elasticity of its capsule are observed in the living subject. Histological examination of the architecture of the spleen reveals it to be admirably adapted to the processes of filtration and concentration of the blood. Receiving its main arterial supply from one of the largest branches of the coeliac axis, it is extraordinarily vascular. Its venous outflow passes through the liver by way of the portal vein. The collateral circulation of the organ, a matter of major importance in certain of the splenopathies, will be mentioned later.

*Function* As suggested by its structure, one of the principal functions of the spleen is the filtration and concentration of the cellular and particulate matter of the blood. This can be readily seen in special

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preparations of the living mouse's spleen with the aid of a dissecting microscope and powerful light (Knisely,<sup>1</sup> MacKenzie<sup>2</sup>)

Closely akin to the sponge-like properties of filtration and concentration is the function of storage. Barcroft and his co-workers<sup>3</sup> were among the first to study this important attribute of the spleen. Using dogs as subjects they were able to demonstrate that the denervated spleen is capable of holding as much as  $1/3$  of the total circulating blood volume of this animal. Furthermore, they found that the normal spleen in dogs contracts in response to such stimuli as fright, shock, hemorrhage, exercise, etc., thus discharging into the general circulation a considerable quantity of stored blood. In the human, similar responses to blood loss, shock, and the injection of epinephrine have been frequently observed at the operating table.

Closely related to these more or less mechanical properties of filtration, concentration and storage are the less well understood effects of the spleen on the morphology and biochemistry of the blood. As a constituent of the reticulo-endothelial system, it seems clear that it plays an important part in the economy of the cellular elements. Following removal of the normal spleen, for example, there is an immediate, though transitory, rise in the blood platelets to a level far higher than that observed after an ordinary laparotomy. From this, and also from the effect produced by its removal in certain of the splenopathies, it is assumed that the spleen is at least in part responsible for the control of the normal platelet level. Similarly, it is known that erythrocytes are destroyed in the spleen, the liberated blood pigments being relayed to the liver for use in the formation of bile and the iron remaining stored in the spleen as hemosiderin.

The fact that in the fetus the spleen plays a hematogenic role is well established. It is also thought that under certain circumstances in the adult this role is resumed, though this is less clear with reference to the erythrocyte series than to the white cell series.

In addition to the foregoing, it is believed that the spleen is concerned in an as yet poorly understood way with immunity and resistance. It should be emphasized, however, that in its every day implication, the resistance of the individual to disease appears to be unaffected by removal of the spleen.

Finally, it is known that this versatile structure is not essential to life. There is good reason to believe, however, that following its removal

TABLE I  
SPLEEN CLINIC—PRESBYTERIAN HOSPITAL

	<i>Cases with Splenectomy</i>	<i>Cases without Splenectomy</i>
Abdominal Buerger's	1	8
Anemia—Aplastic	2	84
Anemia—Cooley's	9	17
Anemia—Sickle cell	2	29
Banti—Extrahepatic—Cavernomatous transformation	5	2
Banti—Extrahepatic—Compression	2	3
Banti—Extrahepatic—Sclerosis of portal veins	5	1
Banti—Extrahepatic—Thrombosis	3	3
Banti—Extrahepatic—Stenosis of portal veins	3	1
Banti—Intrahepatic—Cirrhosis	37	52
Banti—Intrahepatic—Cirrhosis Schistosominal	14	4
Banti—Obstructive Factor Undetermined	27	10
Boeck's Sarcoid	2	6
Cyst of Spleen	1	—
Gaucher's Disease	10	3
Hemolytic Jaundice—Atypical	11	11
Hemolytic Jaundice—Typical	56	20
Hodgkin's Disease	2	172
Leukemia—Chronic Myeloid	1	152
"Normal" Spleen	9	—
Osteosclerotic Myelofibrosis	3	16
Polycythemia	1	110
Purpura—Atypical	10	83
Purpura—Idiopathic Thrombocytopenic	58	26
Sarcoma of Spleen	10	7
Splenomegaly—Undetermined Origin	12	63
Traumatic Rupture of Spleen	15	—
<i>Total</i>	311	883

many, if not most, of its functions are taken over by other organs, notably by those likewise containing elements of the reticulo-endothelial system

In summary, then, the following facts should be kept in mind as the splenopathies are discussed (1) The spleen, in health functions as a filter and reservoir for the blood (2) It is an important, though not essential, member of the reticulo-endothelial system (3) Under certain conditions it has the power both of forming and of destroying the

cellular elements of the blood (4) Its presence is not necessary to the maintenance of life and health (5) The available knowledge of this organ is still very meager

In discussing the splenopathies, some overall figures gathered from the files of the Spleen Clinic of the Presbyterian Hospital and Vanderbilt Clinic will be presented This clinic, headed by Dr Allen O Whipple, has now been in existence for some 18 years Its records include cases undergoing splenectomy at the Presbyterian Hospital as far back as 1916 The longest active follow-up in the material is 26 years

It should be emphasized that the Spleen Clinic has, from the beginning, been a *combined clinic*, i e, its membership is made up of both physicians and surgeons It should also be stressed that the clinic revolves about a central hematology laboratory which is staffed by expert technicians of long experience The role played by these individuals in both the clinical and investigative work of the Spleen Clinic can not be overemphasized and will become self-evident as this discussion progresses Therefore, the data about to be presented and the ideas drawn therefrom are in reality reflections from a pooling of common interests and experience

It will be seen from Table I that the majority of cases subjected to splenectomy fall into three main groups (1) Hemolytic Icterus (2) Idiopathic Thrombocytopenic Purpura (3) Banti's Syndrome, or Congestive Splenomegaly Before taking up these three entities upon which a large proportion of the interest and investigations of the clinic has been centered, it seems wise to dwell briefly on certain of the other less common, but no less important, splenopathies

*Trauma* A discussion of splenic disorders would be incomplete without mentioning trauma The spleen, despite its comparatively protected position within the lower margin of the thoracic cage, is not infrequently injured by both direct and indirect violence Its increased susceptibility to trauma and even to spontaneous rupture, in the larger splenomegalies, should not be overlooked Indeed, this may of itself constitute an indication for splenectomy in certain splenic disorders such as in Gaucher's disease and in some of the very big malarial spleens

The obvious danger in the traumatized or lacerated spleen is from hemorrhage When there is the slightest question as to the existence

of this condition, it is wisest and safest to explore the abdomen without delay. This can be done through a small incision and the presence or absence of splenic damage rapidly ascertained. Removal of the organ is indicated if injury is present. Suture or tamponade of the lacerated spleen is impractical, time consuming, and not to be recommended. Splenectomy is simpler, quicker and more certain.

Another important point that should be kept in mind in this connection is the possibility of delayed rupture of, or hemorrhage from the spleen. This occasional, but treacherous complication should be remembered in connection with all cases of left upper quadrant trauma. It may ensue anywhere from one to twenty-one days or more post-injury and is generally the result of slow bleeding into the splenic pedicle or beneath the capsule. When the pressure within the hematoma so formed rises sufficiently to cause rupture, hemorrhage into the free peritoneal cavity may ensue, which, if not recognized in time, may terminate fatally.

*Infection* Suppurative infection of the spleen is extremely uncommon and is seldom diagnosed prior to operation. Drainage of the abscess or splenectomy, when feasible, is indicated.

Tuberculosis of the spleen, while rare, occurs somewhat more frequently in our experience than suppuration due to the common pyogens. It may involve the organ either in the acute miliary form of the disease or in the chronic generalized glandular variety. In the latter it can give rise to areas of calcification within the spleen which are readily seen by x-ray.

*Malignant Disease* It is surprising how infrequently the spleen is involved in malignant disease. Metastases to the spleen from a distant focus are an extreme rarity, despite the organ's intimate relationship with both the blood and lymphatic systems. Primary involvement of the viscus by malignancy is likewise uncommon, if one excludes lymphosarcoma. When the latter is encountered, it is impossible to be sure that the process is actually primary in the spleen. Splenectomy is obviously of little benefit. Radiotherapy on the other hand, is of considerable help in some cases for a variable period of time.

Hodgkin's disease and the leukemias, like lymphosarcoma, can also produce splenomegaly. In the leukemias, especially in the chronic myeloid form, the size of the spleen may reach considerable proportions. Because removal of the spleen is obviously of no help in these



TABLE II

## SPLEEN CLINIC—PRESBYTERIAN HOSPITAL—SPLENECTOMIES

	Cases
Abdominal Buerger's	1
Anemia—Aplastic	2
Anemia—Cooley's	9
Anemia—Sickle cell	2
Banti-Extrahepatic—Cavernomatous transformation	5
Banti-Extrahepatic—Compression	2
Banti-Extrahepatic—Sclerosis of portal veins	5
Banti-Extrahepatic—Stenosis of portal veins	3
Banti-Extrahepatic—Thrombosis	3
Banti-Intrahepatic—Cirrhosis	37
Banti-Intrahepatic—Cirrhosis Schistosomal	14
Banti-Obstructive Factor Undetermined	27
Boeck's Sarcoid	2
Cyst of Spleen	1
Ganther's Disease	10
Hemolytic Jaundice—Atypical	11
Hemolytic Jaundice—Typical	56
Hodgkin's Disease	2
Leukemia—Chronic Myeloid	1
"Normal" Spleen	9
Osteosclerotic Myelofibrosis	3
Polycythemia	1
Purpura—Atypical	10
Purpura—Idiopathic Thrombocytopenic	58
Sarcoma of Spleen	10
Splenomegaly—Undetermined Origin	12
Traumatic Rupture of Spleen	15
<i>Total</i>	311

conditions, and if performed may well lead to disaster, it is particularly important to distinguish enlargements of this type from other splenopathies benefited by splenectomy

*Erythrocytic Dyscrasias* While splenomegaly is the rule in polycythemia vera and in Cooley's anemia, splenectomy for either condition is valueless. In sickle cell anemia the reverse of splenomegaly occurs when the disease has been present for a considerable period of time the spleen atrophies and may disappear altogether. This interesting phenomenon is still completely unexplained.

TABLE III

	<i>Splenec- tomies</i>	<i>Died foll operation</i>	<i>Died of Disease</i>	<i>Died Other Cause</i>	<i>Total Deaths</i>
Hemolytic Icterus	56	3	1	5	9
Idiopathic Purpura	58	0	4	5	9
Banti's	96	11	28	4	43

*Splenopathies Benefited By Operation* As mentioned earlier in this paper, the splenopathies in which the results of removal of the spleen have been most satisfactory are (1) Hemolytic Jaundice, (2) Idiopathic Thrombocytopenic Purpura and (3) Banti's Syndrome (Table II)

In the first, or hemolytic icterus group, the results of splenectomy have been in general excellent. While there have been three post-operative deaths and five deaths from other causes, there has been but one death from a persistence or recurrence of the disease in a total of 56 cases (See Table III)

The results in the second, or purpura group, while extremely good have not been as uniformly excellent as in Group I. It will be noted that out of fifty-eight patients undergoing splenectomy, there have been four deaths from a recurrence of the disease, and five deaths from other causes, but no operative fatalities.

In the third, or Banti's group, the results, while least satisfactory are definitely encouraging in certain of the sub-groups as will become apparent presently.

*Hemolytic (Spherocytic) Icterus* This disease is characterized by a variable jaundice, anemia, weakness, splenomegaly and above all else by the associated finding of the spherical microcyte in the blood.<sup>4</sup> A family history of the condition is usually, but not always obtainable. In most instances the ailment is first noted in childhood. It runs a chronic course, subject, in the severer forms of the disease, to acute hemolytic "crises" in which the anemia and jaundice become profound. Of interest is the occurrence of gallstones in 40 to 60 per cent of all cases. These are essentially pigment calculi and are due to the excessive blood pigment released by the increased red cell destruction. Splenectomy effects a permanent arrest in practically all cases.

TABLE IV

	<i>Splenec- tomies</i>	<i>Died foll operation</i>	<i>Died of Disease</i>	<i>Died Other Cause</i>	<i>Total Deaths</i>
Atypical Hemolytic Icterus	11	4	1	—	5
Atypical Purpura	10	2	3	—	5

As intimated previously, the *sine qua non* of diagnosis rests upon the finding of the spherical microcyte in the blood smear. This is as essential to establishing the identity of this syndrome as the malarial parasite is to malaria. For while increased fragility of the red cells and a reticulocytosis must be present also, splenectomy can be counted upon to be of benefit only when the spherocyte is present too. To put it another way, we have a sizable group of atypical hemolytic icterus cases, similar in almost every respect to the true disease save for the absence of the spherocyte. The results of splenectomy in this group (See Table IV) have been uniformly disappointing: five patients are now dead out of eleven.

*Experimental.* Spherocytic jaundice can be produced in animals—notably mice—by the intraperitoneal injection of a hemolytic serum prepared by inoculating rabbits with red cells of the mouse. Thus an anti-mouse red cell serum is formed which, when injected into the mouse, produces hemolysis. The spherical microcyte is a phase in the hemolysis of the red cell and is seen in profusion in the experimental animal treated this way. The spleen of the latter rapidly enlarges and on fixed section bears a striking similarity to the histopathology of this condition in the human spleen. Furthermore, when these spleens are studied by the transillumination technique on living mice, it can be seen that the spherical microcyte is selectively filtered from the blood stream by virtue of the fact that its globular shape now prevents it from passing readily from the pulp spaces into the venous sinuses and collecting veins (Whipple<sup>5</sup>). By analogy this would seem to explain Thompson's<sup>6</sup> finding in the spleens of individuals with hemolytic icterus that there is a great increase in the number of spherocytes in the pulp spaces as compared to the numbers found in blood from the splenic vein. The engorgement of the spleen with these cells would, in turn, partially

account for the splenomegaly seen in this condition

If it is admitted that the spleen destroys these spherocytes, which seems obvious, the explanation of the increased red cell destruction and hence the jaundice and anemia of hemolytic icterus is evident. Further evidence in support of the foregoing is found in the fact that following splenectomy in this condition the patient is clinically cured as far as anemia, weakness and jaundice are concerned, but the spherical microcyte persists throughout life. In the only instance of recurrence of this clinical condition following splenectomy in our series, countless small spleens were found scattered about the peritoneal cavity and left upper quadrant at autopsy. We believe that this, in turn, may have been due to the leaving behind of accessory splenic tissue at operation.

*Idiopathic Thrombocytopenic Purpura Hemorrhagica* The results of splenectomy in thrombocytopenic purpura are not quite as good as in hemolytic icterus, nor is the disease as well understood, but in the so-called idiopathic variety many brilliant and life saving arrests have been effected by the performance of this operation.

In the adult, this condition is essentially a disease of the female; there are only four instances of its occurrence in males in our entire series of fifty-eight and in only one of these was the patient over twenty when the disease was first noted. In childhood purpura is usually a self-limited condition and is apt to be associated with infection. Splenectomy is generally not necessary in this age group.

The diagnosis of idiopathic purpura is often difficult. It is easily confused with aplastic anemia or aleukemic leukemia. Because it may occasionally be an allergic manifestation, in taking a history, a careful investigation of the possibility of drug idiosyncrasy or exposure to heavy metals should be carried out. Possible foci of infection in the teeth, tonsils or accessory nasal sinuses should likewise be looked for. In this connection it is interesting that we also have on record several instances of thrombocytopenic purpura resulting from, or secondary to, the invasion of the bone marrow by metastatic carcinoma.

In the female, menorrhagia is a frequent and distressing symptom. The most dangerous sign in either sex, however, is evidence of bleeding into the brain as suggested by headache, coma or dimness of vision. While bleeding may occur in any organ or tissue, it is most commonly encountered in the skin and from the nasal, gingival and uterine mucous membranes.

It is of considerable importance to call attention to the fact that in the majority of cases the spleen can not be felt. It is our belief that the presence of a palpable spleen militates against the diagnosis of idiopathic purpura. In a few of the longstanding cases, however, its tip can sometimes be felt. At operation the organ is generally seen to be only slightly larger than normal.

The characteristic blood finding is, of course, a marked diminution in the number of the platelets which may even be absent on direct examination. In addition to this, there is an anemia which is proportional to the severity of the blood loss and a prolonged bleeding time. While the clotting time is not abnormal, clot retraction may be delayed. The white blood count is either normal or slightly elevated. If this determination is depressed, one should be immediately suspicious of an aplastic anemia, aleukemic leukemia, or some other underlying condition to which the purpura is secondary. Another important diagnostic aid is the measurement of the state of resistance of the capillaries which is definitely lowered in this disease. This may be done either by the suction method of Dalldorf or by the tourniquet test. We have preferred the former,<sup>7</sup> inasmuch as the resistance can be more accurately quantitated with it than with the latter.

It has been the policy of the Spleen Clinic to operate upon these patients during a remission of their disease when possible. One must be prepared to use liberal quantities of blood. Speed is essential during the first part of the operative procedure or, at least up until the time that the splenic pedicle has been clamped and the organ removed.

It will be noted that in the atypical purpuras the results have been uniformly poor. Five patients out of ten in this sub-group are dead. This is due to the fact that subsequent to operation these patients were discovered to have thrombocytopenic purpuras which were secondary to a previously unrecognized underlying disease. The lesson learned from this group is the obvious necessity for being absolutely sure of the diagnosis before proceeding with surgery.

*Banti's Group (Congestive Splenomegaly)* Rousselot and Thompson<sup>8</sup> demonstrated the presence of the congestive factor in the etiology of this condition in dogs and have repeatedly emphasized its importance in man. We have broadly classified the cases which fall into the Banti's group into three categories, depending on the location of the site of obstruction. (1) Extra-hepatic obstruction. (2) Intra-hepatic obstruc-

TABLE V  
B AND II GROUP SUBDIVIDED

	Splenectomies	Deaths
(A) <i>Extrahepatic</i> (Portal Vein Pathology)		
1 Cavernomatous Transformation	5	4
2 Compression	2	1
3 Sclerosis	5	3
4 Stenosis	3	2
5 Thrombosis	3	0
	—	—
	18	10
(B) <i>Intrahepatic</i>		
1 Cirrhosis	37	25
2 Cirrhosis Schistosomal	14	2
	—	—
	51	27
(C) <i>Cause Undetermined</i>	27	6 (3 of other causes)

tion (3) Obstructive factor undetermined

Each has essentially the same disease picture—a big spleen usually hepatomegaly as well, and a blood picture showing depression of all the formed elements of the blood. Ascites and hematemesis are present in advanced cases and of a very poor prognostic omen.

It will be noted from Table V that the results are least satisfactory in the identifiable extra-hepatic group and in the Laennec type of cirrhosis in the intra-hepatic group. Best results have been obtained in those cases in which the obstructive factor was undetermined. In this latter group the liver has been essentially normal in all cases and we believe that this is the reason why the results in this group have been so good. In the Laennec type of cirrhosis group, almost all the patients who are now dead had either hematemesis or ascites. It may well be asked whether operation is justified in this group, when the results of splenectomy are so poor. In order to answer this problem Dr. Mary White<sup>9</sup> of our clinic compared the length of life in these cases following splenectomy with an equal number of unoperated cases of Laennec's cirrhosis proven at autopsy. She found that those who had their spleens removed lived between 3 and 6 years after the development of evidence

of cirrhosis. On the other hand, in the unoperated series of cases coming to autopsy, the length of life after the development of first symptoms of cirrhosis was only  $13\frac{1}{2}$  months. It would seem, therefore, that in this group we are justified in splenectomy, not only as a measure of establishing with certainty the diagnosis but also, obviously, as a method of prolonging life. It should be noted that in the Schistosomal cirrhosis group the results are comparatively good. We believe that the reason for this is the fact that patients with this particular condition show no clinical or laboratory evidence of hepatic insufficiency. At the present time, Doctors Blakemore<sup>10</sup> and Whipple<sup>11</sup> are attempting to short-circuit the obstructed portal system by means of anastomosing the splenic and renal vein, or by the performance of an Eck's fistula. They have performed one or more of these operations fifteen times, with two deaths. As yet the follow-up on these cases is too short to evaluate accurately the results of this type of surgical attack.

#### SUMMARY

In summary, then, the experience of the Spleen Clinic indicates that the removal of the spleen is followed by excellent results in hemolytic icterus, particularly as far as arresting the disease process is concerned. In the thrombocytopenic purpuras, an arrest may be expected in approximately 85 per cent of the cases. In Banti's syndrome, while the process continues to a fatal termination in the majority of those with an extra-hepatic obstructive factor, or a Laennec's type of cirrhosis, life expectancy is increased from 2 to 5 years in this latter group. In those cases where the obstructive factor is not determined and the liver is normal, and in the group caused by Schistosomiasis, the results are very good providing hematemesis or ascites has not developed prior to operation.

In conclusion, may I emphasize (1) the importance of studying these diseases in a combined group, (2) the absolute necessity of accurate hematologic data, (3) the inadvisability of delaying surgery, in those groups where it is indicated, once a definite diagnosis has been reached.

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## HEMORRHAGE IN THE VIABLE PERIOD OF PREGNANCY \*

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VAGINAL bleeding, at any period of pregnancy, is abnormal although it is recognized that there may be some staining in the very early months of pregnancy at the time of the normally expected menstrual period. This may be physiological, before the formation of the placenta. Any bleeding thereafter is abnormal and requires prompt investigation.

I shall confine my remarks, this afternoon, to the management of bleeding during the so-called viable period of pregnancy.

For statistical purposes, the United States Bureau of Census has adopted three criteria for determining the viability of the fetus: (1) 28 weeks, or more, of gestation, (2) a fetus 1500 grams, or more, in weight, (3) a fetus 35 centimeters, or more, in length. It is rare for a baby, not possessing at least two of the above criteria, to survive. There are rare instances in which gestation is apparently slightly less than 28 weeks, or in which the child does not come up to the specifications of weight and length, and yet, with excellent obstetric and pediatric care, including the use of modern incubators and special premature nurseries, such a child has survived.

In 1933 a report on Maternal Mortality in New York City was published by The New York Academy of Medicine, under the auspices of the Committee on Public Health Relations. This report indicated that the maternal mortality rate for New York City was approximately 57 per 10,000 living births. At that time this Committee stated that at least two-thirds of all maternal deaths were preventable. The factor of preventability was assigned to error in judgment or error in technique on the part of the physician or midwife in approximately two-thirds of all maternal deaths. In approximately one-third of the cases, preventability was charged directly to the patient in not seeking or accepting proper obstetrical care.

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Following this report, the Medical Society of the County of New York appointed a Special Committee on Maternal Welfare. I have been a member of this Committee since its formation and, for the past several years, have been privileged to serve as its Chairman. The function of this Committee is to secure and analyze all data relative to ante partum, intra partum and post partum management of all deaths occurring in the viable period of pregnancy.

During the intervening years, I am happy to report, there has been a steady decline in the maternal mortality rate in New York City, and also, that similar Committees are functioning in many of the larger cities and in other less thickly settled districts.

The United States Bureau of Census files, for the year 1929, reported 77 mothers lost per 10,000 live births. In 1944, the United States Bureau of Census files showed a maternal loss of 23.3 per 10,000 live births. And in the same year, the Bureau of Records of the Department of Health for New York City recorded 124,395 deliveries (at 28 weeks of gestation, or over) with 165 puerperal deaths among women who had reached the 28th week of pregnancy. This represents a mortality rate of 13.3 per 10,000 births in the viable period of gestation for New York City. Since the maternal death rate for New York City is not computed on an identical basis with the Census Bureau figures, absolute comparison must not be made. However, a definite trend toward a lowered maternal mortality is evident.

In general, this lowering of maternal mortality in the United States has been due to the marked lessening of death caused by sepsis and the toxemias of pregnancy. In 1943 the Bureau of Census showed, for the first time, that hemorrhage was the major cause of maternal death in the U.S.A. For a number of years hemorrhage had been the major cause of death in New York County, and is still a major, or contributing factor in at least one-half of all obstetrical deaths in New York County.

It is gratifying to note, however, that hemorrhage is being more promptly and adequately treated, largely due to the cooperation and the facilities of the Blood and Plasma Exchange with its various branches located in the hospitals of New York County. It is still unfortunate that a number of mothers do not avail themselves of the existing facilities for proper prenatal and intra partum care and it is also unfortunate that obstetricians have not more promptly and completely utilized the excellent facilities of the Blood and Plasma Exchange.

Although the maternal death rate for New York City, during the year 1944, was considerably less than one-third the maternal death rate in 1933, we must concede that it is possible to reduce still further this maternal loss, especially in cases due to hemorrhage. I believe it is fair to say that the greater number of hemorrhagic deaths are preventable, if prompt and adequate measures are taken. I do not consider that all hemorrhagic deaths are preventable.

Vaginal bleeding, occurring at any time during the viable period of pregnancy, requires most careful consideration. Under ideal conditions the bleeding patient should be placed under the supervision of a well trained physician or obstetrician, preferably in a well equipped obstetrical department of a hospital. Minor degrees of bleeding may require no further treatment and the cause itself, whether from cervical erosion, rupture of small varicosities in the genital tract or excess activity on the part of the patient, may be in doubt.

The more serious types of bleeding may be due to (1) cervical lesions, such as excessive erosions, or malignancy, or, more rarely to a ruptured varicose vein, (2) placenta previa, (3) premature separation of the normally situated placenta, (4) trauma from delivery, with lacerations of the vagina, cervix, or rupture of the uterus, (5) post partum hemorrhage due to uterine atony, fibroids, etc.

Preparation for the control and complete management of the bleeding patient is of prime importance. As soon as the patient presents herself for ante partum care, she should be given a complete physical examination and, in addition, blood should be taken for Wassermann test, hemoglobin content (if this is below 70 per cent a red blood cell count should be made) and the blood should be typed, as to the blood group, and an Rh factor determination should be made. If blood replacement becomes necessary at any time in a mother who is Rh negative, she must receive Rh negative blood. Much valuable time will be saved if the type and Rh factor of the patient is known, prior to the need for transfusion.

Examination for the determination of the cause of bleeding should, of course, be performed under sterile precautions.

#### CERVICAL LESIONS

Bleeding from cervical erosions, or small ruptured varicosities of the cervix during pregnancy, usually requires no treatment beyond rest or

occasional packing or superficial electro-coagulation. Suspicious areas of erosion require biopsy to exclude malignancy. If malignancy of the cervix is found during the viable period of pregnancy, that pregnancy should be terminated as soon as possible, since it is well known that gestation hastens the growth and spread of the malignant process. Delivery of a viable baby through such a cervix is dangerous. The baby should be delivered by abdominal caesarean section, preferably of the Porro type. The amputation of the uterus should be above the bladder fold of peritoneum and without displacement of the bladder. In from four to six weeks the cervical carcinoma can be treated, in the usual manner, by radium and/or x-ray therapy.

#### PLACENTA PREVIA

Placenta previa is one of the major causes of serious hemorrhage in the viable period of pregnancy. The incidence of this condition is probably about one in two hundred deliveries. In the larger obstetrical services this incidence is somewhat greater. The maternal mortality rate in this condition has been stated to be 10 to 20 per cent. In recent years, however, this has been markedly decreased, especially in the larger obstetrical clinics. A review of the literature would indicate that maternal mortality attributable to placenta previa in the past ten years is approximately 3.6 per cent.

The earliest intimation of placenta previa is painless bleeding. This may be a mere spotting or a profuse hemorrhage. Painless bleeding of even minor degree is a danger signal and should not be disregarded. Any bleeding in the last trimester of pregnancy is abnormal. Vaginal examination under home conditions and without proper facilities to combat hemorrhage and carry out proper treatment is dangerous. The patient should be hospitalized immediately so that sterile vaginal examination, on which final diagnosis depends, may be safely made. This examination should be made only after all is in readiness to control hemorrhage and to carry out the proper method of delivery, the only exception to this rule being profuse vaginal bleeding which may be controlled temporarily at least by vaginal tamponade, preferably with heavy iodoform gauze packing. Upon admission, the patient should be immediately prepared for delivery either vaginal or abdominal. During this time she should have a complete blood count, including cross matching and Rh factor determination. A suitable, compatible donor or compatible

bank blood should be immediately available in the operating or delivery room. Meanwhile, the patient should receive supportive treatment with pooled plasma, glucose or saline solution, if needed. Rectal examination is unreliable, inconclusive and frequently more traumatic. The risk of increased hemorrhage and possible sepsis involved in vaginal examination has led to the use of x-ray as an aid in the diagnosis of placenta previa. Many obstetricians are still somewhat skeptical of the accuracy of this method. It appears to be particularly valuable in ruling out premature separation simulating placenta previa. Absolute certainty of diagnosis in placenta previa is obtained only from vaginal examination when the placenta may be felt in the lower uterine segment. The placenta may completely cover the os uteri or may partially cover it. In the less complete type, the edge of the placenta may be felt on the lateral surface of the lower uterine segment when the examining finger is inserted through the cervical canal. Active treatment should be instituted only after the actual diagnosis is made. From the standpoint of treatment there are two types of previa. Either the placenta covers the os (central or complete previa) or it does not (incomplete, partial or lateral previa). The degree of previa, whether complete or partial, will vary with the time of the examination and the relative dilatation and retraction of the cervix.

In the so-called complete or central previa there is little disagreement as to the method of treatment, this method being delivery by the abdominal route, some obstetricians favoring the classical caesarean while others adhere to the low flap type of operation. Obstetricians who favor the classical caesarean in cases of central placenta previa apparently do so on the grounds that the incision in the fundus avoids the placental site and thereby lessens blood loss at the time of operation. Other obstetricians favor the low flap type of caesarean on the grounds that the incision can frequently be made above the edge of the placental insertion, or if this is unavoidable, that the hemorrhage caused thereby is rarely excessive. It is a well known fact that the low flap type of caesarean section has a lower mortality rate than the classical section. A study of caesarean section mortality from all parts of the country covering thousands of cases clearly indicates that the mortality rate in the low flap type caesarean is approximately one-half or less than one-half the mortality rate in the classical caesarean section. This is true in all groups of caesarean sections including caesarean sections

done in cases of placenta previa

When the placenta previa is not complete (probably two-thirds of all cases) opinions as to the method of treatment show considerable variation. An analysis of the literature in the past ten years indicates that two methods of treatment have given the best prognosis for mother and child. These methods are (1) Simple rupture of the amniotic sac (and await the normal process of labor and delivery per vagina) or, (2) Abdominal delivery by caesarean section. The choice of method will be determined by the individualization of each case indicating to the trained obstetrician the proper method to be chosen. This selection of the method of treatment and delivery should be made at the time of vaginal examination. From this moment on active treatment should be decisive and prompt. The general condition of the patient (anemia, parity, etc.) and the viability of the fetus are two important factors aside from the type of previa present. There is no expectant treatment of placenta previa. This rule, however, like all others in medical or surgical therapy, is subject to a somewhat liberal interpretation under the careful supervision of a trained obstetrical surgeon. For example, an elderly primigravida, having only slight spotting without labor and the fetus not yet certainly viable, might be given expectant treatment. This treatment being continued hospitalization, supportive treatment if indicated and with everything in readiness for prompt, active treatment should this become necessary.

All types of accouchement forcé are unqualifiedly condemned in the treatment of placenta previa. In the management of this condition the essentials in all cases are to stop the bleeding and empty the uterus as quickly as is consistent with the least contamination, shock or trauma. We must salvage the mother at all costs and the child also if this is possible and the child is viable.

Other methods of treatment and delivery are extensively used in many of our clinics—Braxton Hicks' version, hydrostatic bag (followed either by forceps or internal podalic version), breech extraction, Willett's forceps or vaginal tamponade during dilatation. None of these methods is free from danger and none has given the low mortality rate both to mother and child, that has been obtained by the simple rupture of the membranes or delivery by caesarean section. The time of treatment in placenta previa is of paramount importance. Hemorrhage occurs during the stage of cervical dilatation and retraction. This hemorrhage

can be controlled in the great majority of cases by any one of the many methods mentioned or now in general use, the fact being that maternal deaths rarely occur before the delivery of the child since, by any of the methods described, pressure is exerted against the abnormally situated placenta and acts as a tampon to control hemorrhage

However, when the uterus has been emptied of the child and the placenta, there is a very great tendency to profuse blood loss. The placenta having been attached to the thinned non-contractile lower uterine segment, bleeding continues from the placental site even though the fundus may be well contracted

In our clinic, we have based our treatment on the avoidance of cervical dilatation and retraction and have found that blood loss, both before and after the emptying of the uterus, is greatly lessened. This avoidance of cervical dilatation can be accomplished only by early caesarean section. If the diagnosis of placenta previa is made, after the cervix is well advanced in dilatation and retraction, particularly in a multipara with a partial or lateral previa and a baby of questionable viability, then vaginal delivery might be chosen, the method of treatment being simple rupture of the membranes allowing the presenting part to descend and make pressure on the placental site

It has been our practice to insert a tight uterine tamponade in practically all cases of placenta previa immediately following the emptying of the uterus, either from above or below

#### PREMATURE SEPARATION OF THE NORMALLY SITUATED PLACENTA

Separation of the placenta from its implantation in the uterine wall results in hemorrhage, either concealed (when there is no escape of blood from the cervix) or manifest (when the blood does escape from the cervix). The incidence of premature separation of the placenta as determined from a review of the literature, indicates a wide variation since many authors include only the two more severe types, such as *ablatio placentae*, while others include all degrees of premature separation, many of which are diagnosed only at delivery when there may be an unusual amount of old blood clot found behind the placenta. If all degrees are included, the incidence is approximately one in 150 to one in 200 deliveries, the more severe types accounting for probably less than one-third the total number

External bleeding may or may not be an early sign of premature separation of placenta. As the condition progresses there is increased uterine tension causing pain. With the increased retroplacental accumulation of blood, the uterus becomes irritable, the contractions continue until, in the fully developed ablatio placentae, the uterus assumes complete tonicity. Pain is continuous and there is no relaxation of the uterine contraction. The patient may show shock out of proportion to the visible blood loss. Some of the more severe cases of premature separation of placenta show little or no external bleeding until late in the management of the condition. A review of the literature for the past ten years indicates a maternal mortality ranging from 5 to 10 per cent although many larger clinics are able to show a maternal loss of not over 3 per cent. Undoubtedly all maternal loss from this condition occurs in the group of extensive premature separation. This group would include not more than one-third of all cases classified as having premature separation of placenta.

Vaginal bleeding or uterine tonicity and pain are indications for prompt hospitalization. The severity of the symptoms, pain, shock, tonicity of the uterus, the parity of the patient and the evidence of hemorrhage, either concealed or manifest, will determine the method of treatment. In the mild cases, expectant treatment under constant hospital supervision is the method of choice. In all cases, however, the patient should be prepared for delivery, either vaginal or abdominal. Supportive treatment with plasma, glucose or saline should be given as indicated. Complete blood count should be done and all preparations made for the replacement of blood when needed. Repeated blood counts and blood pressure readings, pulse rate, etc. will indicate the progress of the condition. A compatible blood donor or bank blood must be immediately available in the hospital. Sedation with opiates for the control of pain is definitely indicated. The obstetrician however must be constantly on the alert that he be not lulled into a false sense of security from the apparent improvement of the patient due only to the relief of pain, while the underlying causes with increasing hemorrhage and infiltration of the uterine musculature become progressively more severe. In many of the milder cases of premature separation of placenta the area is small and does not progress. Frequently there is a moderate loss of blood and the uterus shows some evidence of irritability but does not become tonically contracted. Symptoms may completely sub-



side or labor ensue without further complication. In those cases in which there is a definite progress of symptoms with increasing pain, shock, uterine tonicity or evidence of blood loss, promptly active treatment is imperative. The choice of active treatment will depend upon parity of the patient, the condition of the cervix, as to its retraction, dilatation and consistency, and the condition of the baby, as to its size, viability or possible intra-uterine death.

When the symptoms are increasing or when there is no improvement from the milder symptoms, the indications are to empty the uterus promptly with as little trauma to mother and baby as is consistent with the condition present. If vaginal delivery is chosen, several methods are available:

- 1 Rupture of the membranes plus the administration of fractional repeated doses of anterior pituitary extract or pitocin and await the progress of labor either spontaneous or with forceps delivery.

- 2 Rupture of the membranes plus the insertion of a hydrostatic bag with the administration of fractional doses of anterior pituitary extract.

To either of these methods a tight abdominal binder of the Spanish windlass type may be added.

- 3 Internal podalic version. This has very limited use and must be restricted to the patient with a completely dilated or easily negotiable cervix. It should never be performed in a tonic uterus and if chosen at all should be reserved for the patient with a small and often dead fetus.

It must be further recognized that if vaginal delivery is chosen as a method of treatment in the management of premature separation of placenta, the obstetrician must be constantly in attendance. He must be alert to the physical condition of the patient and able to gauge accurately the progress of labor as well as the condition within the uterus, since hemorrhage may continue beneath the placenta and infiltrate into the uterine musculature with inevitable production of the utero-placental apoplexy of Courvelaire. In this condition the uterus becomes deep purple, completely tonic, often with tears in the peritoneal surface and extravasation of blood into the peritoneal cavity either through the tears or through the tubes. Such a uterus will not recover and return to normal following delivery.

While these changes are taking place the patient shows increasing shock, evidence of severe anemia and peritoneal irritation. When symptoms are increasing, attempt at vaginal management and delivery must

be abandoned and abdominal delivery carried out at once in the interests of the mother. Under such conditions the child in all probability is already dead, although if abdominal delivery is selected promptly fetal salvage may still be possible.

The failure of labor to be initiated or to progress satisfactorily has led many obstetricians to select abdominal delivery as a method of choice in an increasing number of cases of premature separation of placenta. This is particularly true in primigravidas or in all cases in which the baby is viable and living when the patient presents herself for treatment.

In many cases the cervix is thick, firm and undilated hence not favorable for the prompt induction of labor and vaginal delivery. There is a great increase of fetal loss and often progressive blood loss in the mother together with infiltration and destruction of the uterine musculature during this waiting period. The general condition of the patient becomes progressively worse and the risk of delivery whether vaginal or abdominal increases proportionately. For these reasons our clinic has selected prompt abdominal delivery in all the more severe cases of premature separation of placenta and in many of the less severe but definite cases of premature separation especially in the primigravidas or in the multipara in whom the cervix seems unfavorable for prompt induction of labor and vaginal delivery. No method of delivery should be attempted until the mother has recovered sufficiently from shock through the administration of glucose, plasma and blood as indicated and with opium or its derivatives for the control of pain. In many cases there is marked tendency to hemorrhage following emptying of the uterus either from above or below. This hemorrhage can usually be controlled by the routine use of anterior pituitary extract and ergotrate administered intramuscularly or intravenously. Tight uterine tamponade with heavy iodoform gauze is efficacious in most instances.

If however, all attempts to control the hemorrhage fail, no time should be lost in performing a prompt abdominal hysterectomy the patient being supported by repeated blood transfusions. As in placenta previa, blood transfusion not only during but following delivery is of paramount importance. The obstetrical surgeon must realize that continued blood loss and prolonged shock place the patient in such a depressed and critical condition that recovery becomes impossible in spite of blood replacement. In these tragic cases the obstetrician must

make an important decision. If hysterectomy is to be done, it must be performed before the patient is depleted and in severe shock. Maternal life will be saved by the courageous surgeon who places a higher valuation on the life of the mother than upon the conservation of the uterus for possible future childbearing.

In our clinic, hysterectomy has been reserved for a small group of cases in which there was a severe type of uteroplacental apoplexy of Courvelaire or for cases in which there was uncontrollable hemorrhage following the emptying of the uterus. If the uterus shows ability to contract after it has been completely emptied, even though there is considerable infiltration of the uterine musculature with blood, the uterus will recover completely and may be safely retained. Several instances are recorded in which the mother has had subsequent pregnancy and delivery of a living child, usually by repeated caesarean section.

#### LACERATION OF BIRTH CANAL AND RUPTURED UTERUS

Hemorrhage due to laceration of the birth canal manifests itself usually immediately following the birth of the child. Such hemorrhages may be of a very minor degree and easily controlled by prompt repair. These hemorrhages may follow normal spontaneous labor and spontaneous delivery. Instrumental delivery, version and breech extraction or any of the more difficult types of vaginal delivery predispose to birth canal injury with its subsequent hemorrhage. The best treatment of hemorrhage from birth canal injuries is prevention. No vaginal delivery should be attempted until the cervix is fully dilated and retracted. Instrumental delivery must not be attempted until the head is engaged in the pelvis. No method of vaginal delivery should be attempted until the obstetrician is convinced that major disproportion between the fetus and the maternal birth canal does not exist. An accurate diagnosis as to presentation and position of the presenting part is an essential requisite before operative vaginal delivery is attempted. During her labor, the mother must have been properly supported and prepared by the maintenance of fluid intake, preferably by the intravenous route, and by blood transfusion, in those patients in whom marked anemia exists at the onset of labor. Manual dilatation of the cervix or incision of the cervix carries grave risk of hemorrhage post partum. These procedures have been discontinued by many obstetrical clinics. If done at all, they

must be done only after careful review of all the factors involved. Under these conditions the patient must, of course, receive prompt supportive treatment, blood replacement and shock therapy. Further operative procedures should be carried out only after the patient has responded to these measures.

Following the emptying of the uterus, if there is unusual bleeding a complete exploration of the birth canal is indicated. Proper delivery room equipment with an adequate delivery table, proper lighting facilities and instruments for exposure of the genital canal are prime requisites. Under strict aseptic precautions the perineal area is carefully inspected and all damage noted. The cervix should be fully exposed and if tears are present these can and should be repaired by suture. Packing is usually inefficient and should be relied upon only when the patient's condition is such that further immediate operative procedures can not be carried out.

Rupture of the uterus, either before or during delivery, may manifest only minor external bleeding while there is evidence of blood loss and shock out of proportion to the external bleeding. The best treatment for rupture of the uterus, as in other childbirth injury, is prevention. Patients who have had extensive operations on the uterus from previous myomectomies, previous caesareans, etc. should not be allowed to undergo the strain of labor. The dictum, "Once a caesarean always a caesarean," is probably an excellent one. It is possible, however, that previous caesareans may have been done for placenta previa in women who have an adequate pelvis with no obstruction in the soft parts and without fetal disproportion. Under careful supervision of labor and with a favorable soft cervix, the presenting part well in the pelvis and a short labor, vaginal delivery may be indicated.

Prolonged labor without definite progress and advancement of the presenting part resulting in a thinning of the lower uterine segment and a formation of so-called Bandl's ring predisposes to rupture of the uterus. The use of oxytocic drugs, such as anterior pituitary substance to hasten the progress of labor and force the expulsion of the fetus is a frequent cause of uterine rupture. The use of oxytocics before the birth of the baby must be undertaken only after the careful evaluation of all conditions present. Many obstetricians forbid the use of oxytocics until the birth of the baby. If used at all fractional doses repeated only at intervals and for a very limited time are allowable. Oxytocics must

not be used in any labor in which there is even a minor degree of disproportion. They should never be used in the presence of abnormal presentation.

Attempts at operative delivery through an incompletely dilated and retracted cervix are a major contributing factor to extensive cervical laceration and rupture of the lower uterine segment. Version and breech extraction, particularly in the uterus after prolonged ruptured membranes or in a uterus that is tonically contracted, are a frequent cause of uterine rupture. Attempts at instrumental rotation high in the pelvis, particularly, if the cervix is incompletely dilated, may result in rupture of the lower uterine segment.

If uterine rupture is suspected or diagnosed prior to the birth of the child, no attempt should be made at vaginal delivery. Delivery should be accomplished through the abdomen after proper supportive treatment to the mother and with adequate blood and plasma available at operation and post delivery. Many cases of uterine rupture are not diagnosed post delivery, particularly in those cases which show only a small amount of vaginal bleeding. These patients are frequently returned to their beds and in a short time or in a few hours show evidence of shock or blood loss or peritoneal irritation. Frequently these patients receive treatment both too little and too late for maternal salvage. These tragedies could be avoided if careful evaluation of the conditions had been made immediately post delivery. All patients who have had any of the more difficult or complicated vaginal operative deliveries such as instrumental rotation, difficult forceps, face presentation deliveries, version and extraction or breech deliveries or who have had prolonged and difficult labor should have careful immediate post partum examination. As soon as the uterus has been emptied of baby and placenta, careful inspection should be carried out under aseptic precautions and in a well equipped delivery room with all needed equipment available. The freshly gloved hand should explore the genital tract from perineum to fundus. I believe that this exploration should start at the fundus. Particular attention should be given to the lower uterine segment and to the cervix. This should be not only palpated but visualized. If lacerations in the cervix extend deeply into the fornices, these may be repaired by suture and the vagina subsequently tightly packed with iodoform gauze. If lacerations extend deeply into the lower uterine segment or an actual rupture is found in the uterus, the patient should be immedi-

ately subjected to laparotomy. Naturally, this operation should not be made in the presence of shock. The patient must be supported and restored by free administration of blood and plasma. At the time of laparotomy only the more minor degrees of injury to the uterus should be repaired by suture. All more major injuries will necessitate hysterectomy for the control of bleeding and the prevention of infection. Maternal mortality from ruptured uterus has been greatly lessened in all clinics where this apparently more radical treatment has been the method of choice.

### UTERINE ATONY

Postpartum hemorrhage may occur following an apparently normal delivery, such hemorrhage not being due to trauma in any form. This may occur in the absence of any lacerations. This hemorrhage occurs as a rule shortly after delivery although it may occur later in the puerperium. Uterine fibroids interfering with the proper separation of the placenta or complete contraction of the uterine musculature following delivery, predispose to such hemorrhage. Prolonged labor or inefficient uterine contractions predispose to postpartum hemorrhage. Overdistention of the uterus due to twins or hydramnion may be a factor in postpartum hemorrhage. Incomplete separation of the placenta or retained fragments of placenta are causes of postpartum bleeding. A rare but dramatic cause of postpartum bleeding is puerperal inversion of the uterus. Treatment of these conditions will vary somewhat as to the cause of bleeding. Preventive treatment is of prime importance. Supportive treatment of the mother during delivery, particularly with parenteral fluids, blood and plasma if indicated, help to maintain tonicity of the uterus. The excessive use of various analgesics during labor must be carefully guarded against. Textbooks on obstetrics for many years have taught that the placenta should not be expressed for some time usually from fifteen to twenty minutes or even one hour following the birth of the baby. It would seem that the placenta is separated much earlier than this and that blood loss is greatly lessened by its prompt removal. Certainly, in all cases following unusual or continued bleeding following the birth of the baby the placenta and membranes should be removed promptly. Under careful aseptic technique in a well equipped modern delivery room manual exploration of the uterus is safe immediately following the birth of the baby. This should always be done at the

placenta is not and cannot be promptly expressed. Many clinics are now using preparations of ergot, such as ergotrate, ergonovine or posterior pituitary extract or a combination of both immediately following the birth of the baby. Some obstetricians give intravenous ergotrate as soon as the shoulders are in the introitus. The contraction which follows this probably separates the placenta along with the birth of the baby. In such instances the placenta is either expressed spontaneously or by a gentle pressure on the fundus. The already separated placenta is easily expressed from the cervix and vagina. Further intramuscular ergotrate preparations tend to maintain the tonicity of the uterus. Forcible attempts to express the placenta, especially if the uterus is not contracted, or traction upon the cord may tend toward inversion of the uterus. When acute inversion of the uterus occurs, there is usually profuse hemorrhage and rapid development of shock in the mother. Under these conditions the placenta has usually been separated and removed and the fundus will be found inverted within the vagina or protruding through the introitus. Prompt supportive measures must be instituted with blood and plasma. If the patient is not in shock, gentle attempts at manual replacement are justified and indicated. Should these attempts fail or increased shock symptoms supervene, attempts at replacement must be abandoned and the bleeding controlled, if possible, by tight tamponade. Increased efforts at combating shock are continued with heat, sedation and blood replacement. When the patient has recovered from her shock, attempts may be made, under anesthesia, to replace the uterus manually per vagina. If successful, the uterus and vagina are then packed. If attempts at manual replacement are unsuccessful, abdominal operation will be necessary for the correction of the condition. This should not be done until the patient is sufficiently recovered and is in condition for the operation. This may be from several hours to several days. In all cases in which there is excessive vaginal bleeding or lacerations or inversion of the uterus, bleeding should be controlled before the patient is returned to her bed. Careful exploration of the uterus, complete manual removal of all placental tissue if needed, and the insertion of tight uterine tamponade usually control this bleeding. There are a number of obstetricians who believe that uterine packing is completely inefficient and may even interfere with the proper contraction of the uterus. These men rely on complete emptying of the uterus and administration of oxytocics. In any event,

the patient must be properly supported with fluids and especially blood and plasma. If, in spite of all attempts to control the postpartum bleeding by the above methods, there is continued blood loss, the obstetrician must make a very important decision. Certainly, blood loss must be stopped. Under such conditions prompt abdominal hysterectomy will save maternal life. Too often this life saving operation is delayed to the point where the mother cannot recover, in spite of sufficient blood replacement and control of hemorrhage.

Bleeding during the puerperium may occur from retained fragments of placenta or from other uterine pathology, such as fibroids and the so-called subinvolution of the uterus. If this bleeding becomes alarming, proper methods must be instituted for its control. Placental fragments should be removed by a careful digital and instrumental curettage. Uterine fibroids rarely may necessitate abdominal hysterectomy. A rare cause of postpartum hemorrhage, namely placenta accreta, will have been determined in the time when the patient is examined because of failure of the expulsion of the placenta. If the placenta accreta is complete no significant bleeding will occur since bleeding occurs only after partial separation. Attempts at manual removal of the placenta indicate that there is no normal plane of cleavage between the placenta and the uterine musculature. Under such conditions, continued attempts to separate the placenta may result in perforation of the uterus by the examining fingers. Apparently hysterectomy is the only safe method of treatment in cases of true placenta accreta. Fortunately this condition is rare.

In review, it would seem that if we are to reduce maternal mortality due to hemorrhage we should, insofar as is possible, prevent undue blood loss and if in spite of our efforts blood loss is unavoidable, prompt measures for its control and replacement must be available and utilized. During the pregnancy, the mother should be maintained in the best possible physical condition through proper diet, administration of calcium, iron, vitamins and blood transfusion, if necessary, to combat severe anemias. Early in her pregnancy, the patient should have not only a general and obstetrical check-up, she should also have blood Wassermann, blood typing, hemoglobin or red blood cell estimation and Rh factor determination. The patient should carry with her at all times and take with her to the hospital a record of her hemoglobin Wassermann, blood type and Rh factor. This simple procedure will save



much valuable time and possibly life itself should the occasion arise demanding blood replacement

Patients in the viable period of pregnancy should have competent evaluation of all factors concerned with labor and delivery. During labor the mother should have proper supportive treatment with parenteral fluids, rest and blood or plasma if necessary. We must seek to avoid unduly prolonged labor. No attempt should be made at vaginal delivery until the cervix is fully dilated and retracted and the obstetrician is convinced that no major disproportion exists. Obstetricians should avoid the indiscriminate and excessive use of analgesics and anesthetics. There must be prompt recognition and investigation of all abnormal bleeding—ante partum, intra partum or post partum with early and complete emptying of the uterus following the birth of the baby. Careful selection of the method of delivery best suited to prevent or control bleeding in the individual patient is essential. Early and competent consultation with a qualified obstetrical surgeon should be sought in all cases of abnormal bleeding. Finally, an efficient and fully equipped delivery room organization, including an adequate supply of blood and plasma immediately available will prevent many maternal deaths now attributed to hemorrhage in the viable period of pregnancy.

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# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



SEPTEMBER 1946

## THE MANAGEMENT OF BLOOD PRESER- VATION AND BLOOD SUBSTITUTES \* \* \* †

S HOWARD ARMSTRONG, JR ††

From the Department of Physical Chemistry, Harvard Medical School  
and the Medical Clinic, Peter Bent Brigham Hospital, Boston

THE enormous progress in the use of blood and its derivatives during the years of the war has been based in the main on two preexisting bodies of knowledge each in a different stage of development. The first comprises the elucidation over the previous decades by biological methods of the multiple functions of this fluid. With a few exceptions the war effort has not added significantly to the known number of these functions, whether cellular or humoral. The second comprises the knowledge of the physical and chemical properties of the various substances and structures in which these functions reside.

The concerted application to blood of the methods and findings of a group of fundamental studies both in physics and in chemistry undertaken in the prewar years frequently without reference to immediate

\* An address delivered at the Eighteenth Graduate Fortnight of The New York Academy of Medicine on the "Contributions of the War Effort to Medicine."

The bibliography has been selected quite arbitrarily from the very extensive literature such that a more detailed acquaintance with subdivisions of the field may be acquired from the bibliographies of the individual articles cited.

† Much of the work reviewed has been carried out under contract between various laboratories throughout the country and the Office of Scientific Research and Development. Specific contractual arrangements of the contractors are given in the publication of the individual laboratories.

†† Welch Fellow in Internal Medicine of the National Research Council.



utility, has permitted within a remarkably short time the unprecedented extension of the therapeutic range of several of the functions already known

Therefore, in considering the contribution of the war effort to medicine in the field of blood, I would like to take up with you certain of the techniques used to separate, concentrate and stabilize these functions in the preparations which have been made available to the armed forces in quantities hitherto unattained in military medicine, the range of efficacy of these preparations in conditions varying between shock and virus infections, and the type of property on the basis of which substitutes for blood functions have been appraised \*

### WHOLE BLOOD AND RED CELLS\*\*

The necessity for the respiratory function of hemoglobin in the field treatment of many forms of casualty was well recognized early in the war<sup>2</sup> Many investigations<sup>3,4</sup> on the intravenous administration of preparations of purified hemoglobin have not as yet yielded a completely satisfactory substitute for the function of this pigment in its natural state in the erythrocyte

The transportation, storage and use of erythrocytes in war medicine demand a knowledge of the effect of field conditions on their physical stability Before 1940 there existed essentially two techniques for evaluation of red cell stability For the first of these, namely fragility in hypotonic salt solutions, correlation was inadequate with survival time in the body following transfusion The sole method of measuring the latter property (which is critical in the determination of safety and utility of transfusion) lay in the method of differential agglutination<sup>5,6</sup> This consisted of the transfusion of type O cells into type A or type B donors and the estimation of the proportion of surviving cells at subsequent times by agglutinating the cells of the recipient with anti-A or anti-B isoagglutinin

The development within the last three years of radioactive iron techniques has provided a far more accurate measurement of *in vivo* red cell survival

\* The role of the Subcommittee on Blood Substitutes of the National Research Council both in appraisal and in recommendation directly to the armed forces, together with the varied qualifications of the experts who served as members and consultants, have been described by one of its members in another place.<sup>1</sup>

\*\*In preparing this section, the writer gratefully acknowledges the assistance of Dr J G Gibson, II, and Dr J F Ross

The original studies of Hahn and his colleagues<sup>7</sup> in animals and of Ross and Chapin<sup>8</sup> in humans employed a mixture of radioactive isotopes of iron, prepared by bombardment in the cyclotron of iron phosphide. Subsequently, Evans and his co-workers,<sup>9</sup> at the Radioactivity Center of the Massachusetts Institute of Technology, have developed methods for preparing two separate isotopes by bombardment of manganese and cobalt respectively. The half-life of one of these isotopes is five years, that of the other, forty-seven days. The fact that the first has its principal radiation in the form of x-rays and the second in the form of beta rays (energetic electrons) has been utilized in constructing a Geiger counting chamber with windows specifically sensitive to the radiation of each isotope.

With each isotope there have been developed three products safe for human injection: (1) radioactive iron in the form of ferric ammonium citrate, (2) radioactive hemoglobin derived from the cells of patients who have received radioactive iron, and (3) their red cells containing radioactive hemoglobin.

Despite much earlier work (beginning in 1916 with the addition of glucose to citrated whole blood by Rous and Turner<sup>10</sup>), Ross<sup>11</sup> stated, in 1944, that preservation had "not as yet been developed sufficiently to allow shipment of blood to the battlefronts," nor had the conditions of refrigeration and mechanical trauma most conducive to *in vivo* survival of red cells been established. Several groups, working in collaboration with the staff of the Radioactivity Center of the Massachusetts Institute of Technology, have in the interim by means of radioactive cells<sup>12</sup> studied these conditions with sufficient accuracy to permit the definite establishment of such facts as these—that whole blood should be taken into a chilled acidified citrate solution, and that it should be maintained without deviation from refrigerating temperature from that time until when it is used. Through comparative studies of chemical conditions of preservation, there has been achieved a preservative solution permitting 70 per cent 24-hour *in vivo* survival of red cells following storage for over 20 days. Stabilities of this order led to the airplane delivery from the United States to a Pacific battle-front of whole blood in units greater than half a million, dropped by parachute in expendable refrigerators, in one of the later Pacific campaigns without any reports, despite careful investigation, of severe hemolytic transfusion reactions.

The specifications of the particular preservative used probably do

not represent the upper limit of red cell stability which may emerge from further systematic study of the properties of the red cell structure. For indeed, the substances that have been used in red cell preservation have thus far been chosen to some extent on an empirical basis, and owing to the necessity of the rapid attainment of a practical solution to the problem imposed by the war, systematic investigations of the mechanism of action have been postponed.

Economic considerations arising from the fact that the number of clinical conditions requiring therapy by plasma or its fractions exceed those requiring red cells make it highly desirable in military as well as in large-scale civilian medicine to utilize red cells independent of plasma. Whereas sufficient to admit of use in base or civilian hospitals the *in vivo* posttransfusion stability achieved in separated washed red cells has not yet been comparable to that of red cells stored in the presence of plasma. Thus, field use of washed cells in significant quantities did not occur in this war.

Cells from which plasma has been removed without either washing or addition of other agents show higher stability than washed cells; indeed, high enough to make this procedure of current value in blood banks.

The apparent stabilizing activity of plasma leads to the suspicion that there may be a separable substance in which this property might be concentrated. This possibility has been investigated by Hughes and his collaborators.<sup>13</sup>

The new products containing radioactive iron are being turned to peacetime use in further studies of iron metabolism. They make possible the definition of rates of red cell formation and destruction in the elucidation of the mechanisms of anemias with considerable accuracy, particularly in that differentiation between the two isotopes permits the quantitative study of segments of the cell population of two known ages.<sup>14, 15</sup>

#### PLASMA LIQUID, FROZEN AND DRIED

In contrast to the state of knowledge on the preservation of red cells at the start of the European war, the state of knowledge of the therapeutic efficacy of whole plasma stored either liquid or frozen was sufficiently advanced to permit limited military use well before the entry of the United States. As early as 1941, Scudder and his co-workers of

the Blood Transfusion Association,<sup>16</sup> in collaboration with the American Red Cross and several New York hospitals, collected and shipped to England liquid plasma in an amount which for that time was quite considerable. The initial incidence of bacterial contaminations encountered in the early large-scale operations has been sufficiently reduced by such measures as a closed system of preparation with meticulous aseptic technique that, in 1944, Lozner and Newhouser, in analyzing the results of over 1,700 administrations in Naval medical activities on this continent,<sup>17</sup> concluded that it is safe to preserve plasma in the liquid state at room temperature in moderate climates for periods up to at least two years.

The temperature occasionally obtaining both in ships and tanks set a limit to the field utility of liquid plasma. A chemical step significantly increasing temperature stability is McFarlane's<sup>18</sup> lipid extraction by freezing at approximately  $-20^{\circ}\text{C}$  in the presence of ether, followed by ether removal. Though of value in Great Britain<sup>19</sup> by reason of scarcity of drying equipment, this never was widely used in this country, in part because of the high stabilities attained for field use by drying plasma *in vacuo* from the frozen state. This method was found by Florsdorf and Mudd,<sup>20</sup> in 1935, to produce comparatively little alteration in physical and chemical properties of certain types of proteins. Its adaptation to industrial use, pioneered by such workers as Strumia,<sup>21</sup> and the definition of the conditions of drying and bottling yielding both high stability and short resolution times made possible the preparation of enormous quantities of this convenient, readily soluble, yellow powder from blood collected by the American Red Cross Donor Services throughout the nation.<sup>22</sup> The unit in general use at the end of the war, consisting of the dried solids from approximately 500 cc of plasma packaged with intravenous equipment and sterile distilled water for resolution, was admirably adapted to field use where the bulk of the package was no disadvantage. The general availability of this product undoubtedly proved to be one of the great lifesaving measures in many campaigns of the war.

The incidence of homologous serum jaundice (whose magnitude is not yet defined in the several series available for study) may well increase with increasing size of plasma pools. Transmission is not obviated by drying. The risk of this disease, whose course is not always benign,<sup>24</sup> will undoubtedly influence the peacetime management of collection

and pooling of plasma and, indeed, the indications for its use should satisfactory materials freed of this risk become generally available

The property which gives whole plasma its chief value in acute emergencies of military surgery is the capacity of the proteins to hold fluid within the blood stream by reason of both size and high net charge<sup>25</sup> Plasma albumin, comprising only about one-half of the plasma proteins by weight,<sup>26</sup> contributes four-fifths of the power of plasma to perform this function The other protein components, containing specific substances carrying many other functions and capable of widely divergent therapeutic adaptations, possess this power to a much lesser degree The program of plasma fractionation has had as its aim during the war the large-scale separation, purification, concentration, and stabilization of those components which might prove of value in military medicine, and their distribution for appraisal and use in forms best suited to clinical needs

#### METHODS AND PRODUCTS OF PLASMA FRACTIONATION

To avoid prolonged dialyses (necessary for salt removal in methods based on differences of protein solubility in concentrated salt solution<sup>27</sup>), Cohn and his collaborators<sup>28,29</sup> introduced into large-scale fractionation organic solvents removable by volatilization at low temperature and pressure The low temperature use of organic solvents, although hitherto a systematically unexplored field in protein preparation, had been previously studied here and abroad In 1910, Hardy and Gardiner<sup>30</sup> had employed alcohol-ether mixtures at very low temperatures to precipitate the plasma proteins and remove associated lipoids Alcohol precipitation was one of the steps employed in Felton's procedure for concentration of antipneumococcus antibodies from horse serum in 1926<sup>31</sup> Later, Ferry and his co-workers<sup>32</sup> showed that egg albumin maintained at low temperatures in ethanol-water mixtures could still be crystallized

With increasing experience in carrying out separations, it became apparent that the use of organic solvents at low temperatures had a second advantage beyond easy removability, namely, that in their presence the solubility of plasma proteins could be so reduced at low salt concentrations that specific electrical interactions, usually masked at higher salt concentrations, could bring about more selective precipitations than possible where the salt itself is used as a precipitant and the solubility behavior of various proteins of differing biological function is more nearly alike

Predicated on the assumption that protein molecules of different biological function will to some degree possess different structure, standardization of the various fractions was carried out by means of a variety of physical tools designed (in the main before the war) in laboratories both here and abroad with a view toward the precise measurement of physical and chemical constants of large molecules in terms of which their behavior might be interpreted. Two instruments have been particularly useful. The first is the ultracentrifuge of Svedberg,<sup>33</sup> which classifies large molecules according to their speed of motion in a gravitational field and which in combination with measurements of diffusion or viscosity properties of proteins yields information as to size and shape. The second is the electrophoresis apparatus of Tiselius,<sup>34</sup> which has yielded a classification of the plasma proteins according to their speed of motion in an electrical field, a property which although extraordinarily useful from an empirical point of view is theoretically difficult of precise interpretation.<sup>35</sup> In many instances, methods of measurement now available are not sufficiently sensitive to yield differences in fine structure between molecules of apparently identical size, shape and electrical properties though of divergent functions.

The extension of fractionation from a laboratory glassware stage to an industrial scale, in which the plasma of over two million donors approximating in volume some 120,000 gallons was fractionated, was carried out through the construction of a pilot plant at the Harvard Medical School. To this came chemists from the commercial laboratories for study in collaboration with the pilot plant group of the processes and equipment which were later adopted in setting up the commercial plants. The continuing collaboration between these groups, involving many visits between the staffs of both pilot and commercial plants, was in great measure responsible for the successful use of the fractionation methods as they were developed and modified throughout the war.

The adaptation of the chemical specifications of various products to clinical needs has in turn involved collaboration between the clinical groups responsible for appraisal and the chemical groups responsible for production. In those areas where continuity and closeness in this collaboration have been sufficient to give the clinicians some grasp of the range of chemical properties attainable and the chemists some notion of the nature of clinical phenomena and of the applicability and limitations of quantitative methods in their study, progress toward clinical use

has been usually rapid \*

The results of the fractionation program have been twofold. The first has been the separation and concentration in usable form of the osmotic, the isoagglutinin, certain of the immune, and certain of the coagulation functions of blood. The properties of these products and their uses developed to date have been the subject of many papers ranging from the earlier studies of Janeway and his co-workers<sup>36</sup> on the use of human serum albumin in experimental human blood loss to the studies now in progress on the use of the antihemophilic function of the blood,<sup>37</sup> certain of the more recently studied uses of gamma globulin in prevention of hepatitis<sup>38</sup> and of salt-poor albumin in the treatment of edema of hepatic and renal origin.<sup>39,40</sup> have been discussed in this series of addresses by Dr. Stokes and Dr. Thorn. Further detail on flexibility of properties and uses will not be presented here. The separations that have been made are not uniformly sharp, the aim has of necessity been a combination of sufficient purity necessary for use together with maximum yield. Thus, for example, whereas normal human serum albumin is electrophoretically homogeneous, prothrombin as currently prepared is not so, and the antihemophilic substance<sup>41</sup> has not yet been separated from fibrinogen under conditions which leave each in a usable form.

The second result is to provide in a small number of standardized fractions of plasma and their various subfractions, reagents, or starting materials for preparation of reagents sufficiently pure such that the mechanism of their chemical interactions may be more accurately studied and the conditions governing their equilibrium in the body defined. The currently standard fractions and subfractions are by no means final. Quite a different system of conditions may be necessary to concentrate certain other substances not as yet purified.

### BLOOD SUBSTITUTES

For each of the various functions of human plasma which have been thus separated and concentrated, there usually exist in the comparable tissue of animals substances with similar functions which under restricted circumstances may be made applicable to use in human therapy.

\* Acknowledgment of the large groups of collaborators—both chemical and clinical, will be found in the many recent reviews of Cohn who directed the development of the plasma fractionation program and in two series of articles entitled "Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation" and "Preparation and Properties of Serum and Plasma Proteins," appearing in the *Journal of Clinical Investigation* and the *Journal of the American Chemical Society* respectively.

All proteins of other than human origin are potential antigens. Thus, in the evaluation of any product of heterologous origin to replace the parallel human product in therapy, it must be shown that the danger of reactions based on an immunological mechanism has by reason either of purification, chemical modification, or site of use been obviated.

About the time Wangensteen published the first of his extended studies on the injection of bovine plasma in man,<sup>42</sup> at the suggestion of the late Dr. Walter B. Cannon a systematic study of certain purified animal proteins was initiated. Moreover, in many laboratories various forms of physical and chemical treatment have been used in attempts to modify the antigenicity of foreign proteins without excessive alteration in physical-chemical properties or biological function.

Despite such encouraging early findings as wide variation in antigenicity between several components of plasma of a given species,<sup>43</sup> during the period of the war no products emerging from this work were used in military medicine.\* For this, antigenicity has not been the sole responsible factor.

The evaluation of a substitute for the natural substance performing a given function must be made not only in terms of the adequate capacity to perform the function but also in terms of the other properties, advantageous or disadvantageous, of the substitute substituent material of which antigenicity is only one.

For instance, a substance designed to increase plasma colloid osmotic pressure must be considered with respect to the distribution of molecular sizes and shapes (which will in part determine duration of efficacy), with respect to effect on blood viscosity (due either to intrinsic molecular asymmetry or effect on red cell aggregation), with respect to effect on equilibrium of the various plasma proteins with the tissues, and on the capacity for their regeneration, with respect to distribution and effect on tissues themselves (particularly with reference to "storage diseases"), with respect to nutritional capacity, and ultimately (as in the case of all "blood substitutes") with respect to cost and feasibility of standardized safe production.

Such properties determine the therapeutic scope of a material. Thus, the gelatins, a group of degradation products of animal collagen, have long been known to lack antigenicity.<sup>44</sup> The immediate increases in plasma volume following injection of either human albumin or certain

\* Indeed, no products of other than human origin were recommended to the armed forces by the Subcommittee on Blood Substitutes of the National Research Council.<sup>1</sup>



gelatins<sup>45 46</sup> make these substances comparable in the short-term treatment of shock in the previously healthy patient. Rapid urinary loss (in part by reason of small molecular diameter<sup>47</sup>), together with poorness in certain essential amino acids, makes gelatin far less valuable than albumin in treatment of the problems consequent upon the hypoproteinemia seen in surgical and medical practice.

For products whose route is not intravenous, obviously other groups of properties take prominence in evaluation. Thus, for those which have contact with brain tissue the relation between those physical and chemical properties susceptible of standardization and sequences of tissue response are highly important, antigenicity may prove less so. Indeed, the accumulating surgical experience with bovine thrombin (under certain circumstances highly antigenic<sup>48</sup>) has as yet suggested very little risk attached to its repeated application in the same patient. Its hemostatic use<sup>49</sup> in conjunction with an absorbable matrix, soluble cellulose,<sup>50</sup> is discussed by Dr. Frantz elsewhere in this series of addresses.<sup>51</sup>

There is no question that an increasing group of satisfactory substitutes for blood functions will be of great value not only in the practice of medicine by reason of convenience and economy, but in the development of further therapeutic advances by releasing human material to new investigations.

It is worth pointing out advantages apparently inherent in having systematic study of natural functional substances in a tissue proceed simultaneously with, if not precede, study of "substitutes," either heterologous or synthetic. This pattern of investigation (achieved spontaneously in such fields as endocrinology) has proved peculiarly profitable in the field of blood. It has resulted in the availability of methods for preparation in quantity of many natural materials which, although apparently merely by-products in wartime, may have considerable significance for peacetime therapy. Had the wartime research activity been limited solely to the empirical search for economical substitutes for those therapeutic possibilities of blood most obvious at the start of the war, it is possible that many developments of significance in military surgery (for example, dural substitutes developed from human fibrinogen and thrombin) would have been postponed.

#### PEACETIME BLOOD MANAGEMENT

In that there is no substitute for the human erythrocyte, human

blood must still be collected. The initiation of plans of central collection in connection with state programs of plasma fractionation gives evidence that the Red Cross wartime experience in this field will find continued application.

In the management and distribution of centrally collected blood, group O red cells,\* of known Rh typing and resuspended in a medium yielding satisfactory *in vivo* stability, may prove an excellent standard preparation for large metropolitan hospitals and, indeed, could be shipped to small outlying hospitals for which the maintenance and staffing of the type of blood bank used in metropolitan hospitals is unduly expensive. There will doubtless be sufficient red cells of other types to cover experimental needs in those areas where study of components and functions of erythrocytes is active.

The effect of the shift of emphasis from military to civil medicine on the demand for the various products which have already been standardized in plasma fractionation can not now be predicted with accuracy, chiefly because in many instances the range of clinical applicability is not yet fully explored. For example, attenuation in measles and passive immunization in hepatitis can probably consume as much concentrated antibody-containing gamma globulin from normal subjects as can be supplied, the effect of early massive doses of normal gamma globulin in the prevention of relapse or fatal progression seen in a certain proportion of hepatitis patients is not certain. The effect of enzymatic hydrolysis on cellular penetration of antibody in those diseases where the infectious agent is chiefly intracellular (e.g., rickettsial) has not been thoroughly studied. The preventive and therapeutic possibilities of similarly concentrated gamma globulin of hyperimmune subjects (convalescent from various diseases) are not yet worked out.

Moreover, there are in plasma many substances of possible clinical value which are yet relatively unexplored from the chemical standpoint. Among them are cholinesterase which, if sufficiently concentrated in a preparation suitable for parenteral use, might be of interest in connection with conditions not readily subject to surgical parasympathectomy (e.g., ulcerative colitis), the plasma fibrinolytic enzyme which, if sufficiently purified, might prove free of dangers attending use of current preparations and be suitable for study in subacute bacterial endocarditis.

\* The recent observations of Emerson and his colleagues on hemolysis of recipient cells following transfusion of group O whole blood emphasize the necessity of the removal of isoagglutinins either by chemical means or by separation of the plasma.

is resistant to the combination of chemotherapy and anticoagulants

It is now as impossible to predict where in this group of substances clinical success will be achieved as it would have been to predict the prophylactic success attained in hepatitis with concentrated gamma globulin at the start of the plasma fractionation program

The task of finding appropriate conditions for the separation and purification of substances yet unstudied will fall increasingly on the investigative chemists associated with state and other laboratories engaged in blood processing. There is no assurance that the laboratories which have assumed during wartime a responsibility, often nationwide and controlling, for collaboration between chemical research, production units, and clinical units will continue to carry this responsibility in peacetime beyond an advisory level. Moreover, the value of continuation may well be questioned from the standpoint of the individual scientists involved and the ultimate progress of the fundamental sciences. The extremely rapid development facilitated by the wartime centralized collaboration is to a great extent based on the implications of two decades of investigation, both in the fundamental sciences and the clinic, without such centralization.

As the pressure for immediate utility diminishes and many chemists and physicists turn to the advancement of their own fields, the advances in clinical use of blood will become slower. They are most likely to occur where clinicians, interested in a given group of diseases, have sufficient familiarity with chemical developments to see and assist the chemists to see the potentialities and to utilize the chemists' wisdom in adaptation of products to experimental and clinical requirements and in the control of chemical uniformity, that is to say, in those areas where the clinic is able to assume the principal responsibility for the pattern of collaboration which in the war has proved fruitful under greater centralization.

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## PLANNED CONVALESCENCE\*

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**D**URING the past four years Medicine accepted the challenge of total war and has made great advances which will be a boon to mankind in time of peace. Although they were the most widely publicized, these advances were not limited to science and technology, but were also in the field of human relationship, the bond between the patient and the doctor has had a rebirth. Thousands of doctors and millions of men are returning to their communities with closer bonds than ever before as a result of war experience. The science and art of medicine have become welded inextricably to meet the physical and spiritual needs of man.

This has been particularly true in the field of rehabilitation and convalescent care, where a close patient-doctor relationship became the keystone of the treatment and management of casualties returning from combat theatres. Early in the war when the conservation of manpower made necessary a comprehensive program, in order to reclaim every man possible for the military service, the Army Air Forces formulated a program based on this concept.

In those dark and uncertain days, every man-hour of training was unbelievably important. Flying schools, radio schools and mechanic's schools worked around the clock, twenty-four hours a day, seven days a week. It was necessary for every man to pull his share of the load. Yet, in our military hospitals thousands of men who had completed their definitive medical care sat around waiting for time to complete their convalescence. The hours they spent in boredom without purposeful activity did not contribute to the mission of the Army Air Forces.

## THE AAF CONVALESCENT TRAINING PROGRAM

It was in an effort to provide for the purposeful employment of

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this hitherto wasted time, and to utilize a program of activity as an adjunct to the definitive medical care of the sick soldier, that the Convalescent Training Program was established in all AAF hospitals in December, 1942. The purpose of that program was two fold first, to send the soldier back to duty in the best possible physical condition in the shortest possible time, second, to teach the soldier-patient something that would make him a more efficient and effective fighting man.

Physical reconditioning was accomplished by a systematic, graduated series of calisthenics and corrective exercises. Given at first in their mildest form even to bed patients, the exertion was gradually increased in ratio to the patient's physical tolerance until before returning to duty, he was able to participate in a comprehensive program of drill, hikes, calisthenics, athletics and fatigue duties. Exercises were begun in bed as soon as the patient's condition permitted, to prevent muscular atrophy in the unaffected parts and general deconditioning phenomena. Pneumonia patients were given deep breathing, hand, arm and chest exercises as soon as their temperature returned to normal. Physical activity was as much a part of the doctor's prescription as drugs and diet.

Minds were not permitted to become stagnant. Time formerly wasted in reading comic books and mystery stories was spent purposefully. The classroom was moved into the wards and training films, chemical warfare classes, radio code practice periods, and discussions on "Why We Fight" and "The Postwar World" became an integral part of the hospital day. Radios, carburetors and even airplane engines were brought into the wards and sun rooms. The hospital was transformed into a combination gymnasium, schoolroom, machine shop and New England Town Hall. This program has been made a permanent part of the postwar military medical service.

#### PHYSICAL RECONDITIONING

Early in the convalescent program it was noted that, to obtain maximum results, reconditioning had to start at the earliest possible moment following acute disease or injury. It had to be purposeful, progressive, and graduated as the patient's physical tolerance increased. Special corrective exercises had to be designed to meet specific military needs and experienced physical training instructors were given special instruction on administering them. A positive attempt was made to correlate ward fatigue and detail work with the soldier's disability to

aid in functional recovery. Men with hand, finger and wrist injuries were given fatigue duties that involved finger and hand manipulation. Those with bad backs or knees were given duties which involved bending, stretching, kneeling, lifting, and other movements which aided in strengthening the affected part.

The *Handbook of Recovery*<sup>1</sup> (AF Manual No. 23) was prepared as a prescription blank for all types of orthopedic disabilities. It included a nine-page section on anatomy, physiology and pathology written in simple language to show the soldier-patient why he was in the program, the value and effects of active exercise, how bones, muscles and nerves are made, what happens when they are injured and how they heal. This was followed by a series of two-page prescription blanks for the specific injury, demonstrating to the soldier-patient by diagram the normal function of the injured part, his diagnosis and disability, the type of physiotherapy prescribed, the illustrated active exercises to be done with and without supervision, and a personal objective recovery chart which the patient kept himself. This was an effective innovation as it not only gave the patient an insight into and understanding of his condition, but great motivation through his ability to measure his own progress objectively. An accompanying instructor's manual *Handbook of Physical Retraining*<sup>2</sup> (AF Manual No. 24) was prepared for the guidance and use of the physical reconditioning instructors in order that they might properly administer and supervise the exercises to obtain maximum results.

*Let's Walk*<sup>3</sup> (AF Manual No. 49) was another publication designed for the patient which met with widespread use and approval. Unique in its presentation, this booklet dealt with the functional aspects of walking with the use of aids. It first gave the patient a brief, psychological orientation to his disability and then proceeded to demonstrate objectively, through the use of illustration and charts, the factors involved in walking with aids, the muscles which must be utilized and therefore strengthened to use walking aids effectively, the techniques and gaits of walking, practical hints on care of the aids, and most important insight and motivation.

#### RESULTS OF THE PROGRAM

More interesting, however, and equally as significant as the means used to meet the objectives, were the ends themselves. Some of the



pertinent observations of the Convalescent Training Program after nearly three years of experience were hospitalization time was shortened, hospital readmissions were reduced, sick leaves were eliminated except in extraordinary cases, and the morale of the soldier-patients was immeasurably improved when they were kept busy and interested in purposeful activity

A number of interesting clinical studies were made Van Ravenswaay and his co-workers<sup>4</sup> studied 645 cases of virus pneumonia, all treated in the same acute wards They were then assigned to alternate convalescent wards In Ward I "nature was allowed to take its course" and the men sat around and waited until they and the medical officer felt they were ready for duty In Ward II the patients were kept in bed until their sedimentation rate reached 10 mm in one-half hour and then were put in a reconditioning program, beginning with exercise for one-half hour the first day, and increasing progressively until the twelfth day when the patients were participating in a full six-hour day of physical training, mass games, competitive sports and active recreation including a ten mile hike Group I averaged 45 days hospitalization with a 30 per cent recurrence rate, Group II, at the end of 31 days, was discharged to duty with but a 3 per cent recurrence rate, 45 days hospitalization, unsupervised, 31 days with graduated conditioning—a 30 per cent recurrence rate in the unsupervised compared with but a 3 per cent recurrence rate in the supervised

Karpovich and his associates<sup>5</sup> at the School of Aviation Medicine, San Antonio, Texas, studied a similar group of 200 aviation cadets convalescing from virus pneumonia Using a modification of the Harvard Step Test and starting as early as the first afebrile day, Karpovich found that by the reactions to this test it was possible to determine, with some degree of accuracy, the patient's ability to enter into, and participate in, an active convalescent program An interesting by-product of Karpovich's observations was that patients being tested required five days less hospitalization time than those participating in the general program—pointing out the tolerance and ability of these men to participate in an even more active program with beneficial results

Marquardt,<sup>6</sup> at the AAF Regional Station Hospital No. 1, Coral Gables, Florida, made an interesting observation on a small group of patients recovering from virus pneumonia These patients were clinically well but had residual persistently positive x-ray findings They were

put on hyperventilation every waking hour, twelve times a day, and serial x-rays were made every twelve hours. Over 90 per cent of the patients in the series became x-ray clear in a period of 96 hours.

As a part of the AAF Rheumatic Fever Control Program, Karpovich, Weiss, Starr and Ershler<sup>7</sup> did a study on physical fitness testing and physical training of convalescent rheumatic fever patients. Because of the chronic, recurrent nature of the disease and the possibility of disabling cardiac sequelae, it was felt that special emphasis should be placed on the standardization of physical activity and convalescent training for these patients. This was achieved by working out a series of graduated physical fitness tests which could be used in conjunction with the usual clinical observation to determine the rate by which the patient could safely be permitted to progress to increased physical activity.

Using a modification of the Harvard Step Test with two benches 12 and 20 inches in height, and a cadence of twenty-four steps per minute, physical testing was started when, in the judgment of the medical officer, the patient should be permitted to be out of bed in a chair. The first test involved twelve step-ups in thirty seconds, using the 12 inch stool. Criteria for passing that test were a pulse rate less than 100 per minute one minute after the exercise, and good coordination in performance. If the patient passed this test and the medical officer concurred, he was allowed to be ambulatory in the ward. Using the same criteria, the next test involved twelve step-ups in thirty seconds, using the 20-inch stool. In this test it was found that body metabolism in the average individual was raised eight to ten times. If the patient passed this test, he was placed on a program of graduated ward calisthenics. These exercises were given ten minutes twice daily to start, and continued over a period of approximately three weeks, they were then increased to thirty minutes twice daily. The exercises used at the beginning of this program were found to raise body metabolism roughly three times. The degree of strenuousness of the exercises during this period was gradually increased to a level which raised the metabolic rate seven to nine times the normal.

The next level of physical fitness testing was designated the progressive test, consisting of twenty-four step-ups per minute to a 20 inch bench for a period of five minutes. Scoring was based on the duration of the exercise plus the pulse rate one minute after exercise. If the patient made a minimal passing score on this test and the medical officer in

capped as far as his particular job is concerned. It is not a matter of coddling but one of proper placement. The worker is fitted to the task and knows that a full day's work is expected of him.

Most individuals use less than 10 per cent of their potential efficiencies in normal pursuits. It is only in emergencies that we call upon our tremendous reserves of physical power and ability. In many cases a worker's physical defect acts as a tremendous stimulus to overcompensation, resulting in extraordinary physical ability. Adler developed a complete system of psychology on the basis of inferiority. He believed that the successful, the efficient and the aggressive individual was one who was compensating for some inferiority. The employer of handicapped workmen is putting that psychology into purposeful and gainful application.

Foremen report that handicapped workers are frequently a steady influence in their departments. Their jobs mean more to them than to the normal workers. They have had more difficulty in getting employment and they value the right to work.

#### OFFICE OF VOCATIONAL REHABILITATION

The work of the Office of Vocational Rehabilitation and its participating State rehabilitation programs, has been growing steadily since it was established under the National Civilian Vocational Rehabilitation Act of 1920. Its services were greatly expanded by amendments to the original law by Congress in 1943. Today, under Public Law 113, the disabled civilian can obtain practically the same rehabilitation services as offered to the disabled veteran by the Veterans' Administration under Public Law 16, with the exception of pensions and subsidization of living expenses. The record of the federal-state rehabilitation programs is heartening but when the 43,000 persons who received such service in 1944 are compared to the one and one-half to two million whom the Office of Vocational Rehabilitation estimate are in urgent need of such service, it is woefully inadequate.

The Federal and State vocational rehabilitation programs alone, however, cannot meet our rehabilitation needs. Although they have both the funds and the authority, they are handicapped by the lack of training facilities to which they can refer their cases. These state vocational rehabilitation agencies do not do the actual rehabilitation themselves, but use existing public and private facilities such as schools, vocational

training courses, and on-the-job training on a fee basis

Medical, surgical and diagnostic services are obtained by contract with groups, clinics and private physicians. Hospital care is purchased from existing hospitals. The same is true in physical restoration, which may include any type of medical or allied services that will aid in eliminating or substantially reducing an individual's disability as an employment handicap. These include medical, surgical or psychiatric service, physical and occupational therapy, hospitalization, dentistry, care in a convalescent or nursing home, drugs and supplies, and such prosthetic appliances as artificial limbs, braces, hearing aids, eyeglasses and dentures.

The funds and authority are available, but the facilities equipped for doing the actual job of rehabilitation are inadequate. Several national organizations are making efforts to stimulate public interest in rehabilitation by demonstrating to both the medical profession and the public what actually can be done by an integrated program of physical, mental, social and vocational adjustment.

One such group is the Baruch Committee on Physical Medicine, which is translating the experiences of the armed forces in rehabilitation into its civilian applications, and making this experience available to communities, medical schools, or organizations interested in establishing rehabilitation centers.

The Baruch Committee members have pointed out that rehabilitation cannot be done by segments. If a man has a hearing disability, has lost a leg, or has a cardiac condition, his disability affects all phases of his life. It has a bearing on his vocational opportunities, his family and social life, his recreation and his mental and emotional outlook. Individual disabilities cannot be treated in rehabilitation, the whole man must be considered.

Today there are a few specialized services to the handicapped which are doing excellent work in their limited fields. The number is so small that they can reach only a small fraction of those who need aid. Too many existing programs, however, can treat only one segment of a patient's problems. There is a great need for comprehensive, integrated community centers. Rather than a dozen small agencies each giving individual psychological assistance, occupational therapy, vocational training or social service, aid to the deaf, the blind, the orthopedically handicapped, the patient with a speech defect or arrested tuberculosis,

or the cardiac, there needs to be one large community center where all the necessary services can be integrated to improve the quality and scope of service to the patient

The Baruch Committee has outlined a plan for community rehabilitation centers that will furnish a complete service<sup>10</sup> They have blue-printed a model rehabilitation center outlining its mission, organization components, physical set-up and its relationship to the medical and allied professions—industry, labor, social and governmental agencies—and to the community as a whole The report provides communities with a pattern representing the ideas and experiences of both the armed services and leading civilian institutions and organizations

Preventive medicine and curative medicine and surgery have made great advances Their third phase of medical care—rehabilitation—has been neglected Comprehensive rehabilitation programs have been established in the armed forces The Veterans' Administration is organizing a similar service The disabled civilian in a democracy deserves the same opportunity as the disabled Veteran

It is not enough to get our patients out of bed Our duty, as physicians, is terminated only when our patients are returned to productive living The magnitude of the task is a staggering one, a challenge that must be accepted not only by the medical profession but by the democracy

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## CLINICAL RESEARCH MEETING

*Arranged by the Committee on Medical Education*

JUNE 5, 1946

BERNARD S. OPPENHEIMER, *Chairman*

\* \* \*

*The Clinical Correlation of In-Vitro Penicillin Sensitivity Tests\**ERNA ALTURE-WERBER, PH D., MARY KOZAK SHORE, A B.,  
EDITH C. MENKES, and LEO LOEWY

In-vitro penicillin sensitivity tests of organisms as a rule merely estimate the bacteriostatic activity of penicillin. The information gained from this type of test was not always helpful in establishing optimum dosage schedules for the treatment of diseases caused by penicillin-inhibitable organisms. In actual practice, particularly in the treatment of subacute bacterial endocarditis, merely paralleling in the blood serum the in-vitro penicillin bacteriostatic activity did not consistently achieve effective therapeutic blood levels. As a result of clinical experience, therefore, the dictum was well founded that multiples of five to ten times the in-vitro sensitivity figure were essential for termination of the infection. It was subsequently suggested that "to be therapeutically effective, penicillin blood levels must be far in excess of the in-vitro bactericidal requirements" and that "inadequate dosage invites treatment failure and the organisms may acquire resistance that is so high as to render future therapeutic levels virtually unattainable."<sup>1,2</sup> It was early evident that there is both a bacteriostatic and a bactericidal zone of penicillin activity. While the arbitrary intensification of penicillin dosage in the treatment of subacute bacterial endocarditis was attended with greater clinical success, there were still sufficient treatment failures to justify intensive investigation for

the causative factors. One result of this study was the discovery of a new type of non-hemolytic streptococcus, designated *Streptococcus sbe*.<sup>3</sup> The factors responsible for the refractory nature of this organism are under investigation and are not discernible in test tube studies per se. Laboratory techniques were devised to determine the bacteriostatic and minimal lethal dosage of penicillin for the infecting organisms. The routine use of these procedures has afforded an explanation for the failure of penicillin treatment with seemingly adequate dosage as judged by customary standards. Thus while the infecting non-hemolytic streptococcus of PG, a patient with subacute bacterial endocarditis, had a bacteriostatic penicillin sensitivity of 0.008 Oxford units per cc. of test broth, a seven weeks span of therapy of 300,000 to 500,000 Oxford units of penicillin daily with average blood levels of 0.53 Oxford units per cc. failed to cure. A total of 22.4 million Oxford units was administered during this unsuccessful course of therapy. The answer was found in the determination of the minimum lethal dosage of penicillin for this causative organism, which proved to be 1 Oxford unit per cc. of test broth. When the daily penicillin dosage was lifted to 2 million Oxford units with resultant blood levels of 2 or more units per cc. of serum,

<sup>1</sup>From the Department of Laboratories and the Department of Medicine, Jewish Hospital of Brooklyn.

the blood stream was sterilized and the infection was terminated. That subcurative doses of penicillin have a pronounced tendency to increase the resistance of infecting organisms was apparent in our series of 157 cases of subacute bacterial endocarditis treated with the combination of penicillin and heparin. This fundamental concept, the implications of which are now widely recognized, has been found to apply to infections in general.

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## *Repository Injection of Penicillin in Water-in-Oil Emulsion*

*Effect on Early Syphilis—A Preliminary Report*

ALFRED COHN, THEODORE ROSENTHAL and ISAAK GRUNSTEIN

In previous investigations a method was developed to cure gonorrhea by a single intramuscular injection of penicillin in water-in-oil emulsion. The administration of penicillin in such a vehicle has been now applied for the treatment of early syphilis. It is hoped that this method which reduces the number of daily intramuscular injections to one or two, may open the way for the ambulatory treatment of syphilitic patients with penicillin.

A total of 35 male patients with early syphilitic infections received daily injections of penicillin in water-in-oil emulsion over a period of 5 days. The daily dose ranged from 400,000 to 1,000,000 Oxford units of penicillin, given intramuscularly either at 12 or 24 hour intervals.

After total dosages of 2,000,000 to 5,000,000 Oxford units respectively, definite clinical regression of the syphilitic lesions were observed among all patients at the end of active therapy.

Darkfield examinations initially positive for *Treponema pallidum*, were found negative 24 hours after the initiation of treatment in all of 11 cases examined.

Complete healing of the primary chancre at the fifth day of treatment was noticed in 19 patients and healing within a period of 13 to 90 days took place in 13 cases. Of the remaining 3 patients one showed a clinical relapse when reexamined 65 days after treatment, and the other 2 patients were delinquent.

Complete involution of the secondary manifestations immediately following treatment was observed among a group of 12 patients and within a period of 11 days to 6 weeks in the remaining 3 patients. Similar involution of lymphadenitis occurred either shortly after treatment or 5 to 7 months later.

Titrated Wassermann reactions and flocculation tests (Kahn, Kline and Mazzini) were done on the serum of each patient before treatment and repeated each time the patient reported for reexamination. Four initially negative Wassermann sera remained negative during a period of 1 to 12 months. The positive Wassermann tests of 16 patients reversed to negative within a period of 5 to 28 weeks. The sera of 2 other patients yielded persistently positive Wassermann and flocculation tests over a period of 8 to 10 months, while their corresponding spinal fluid tests done 6 months after treatment, were negative.

The initial spinal fluid examinations of all patients before treatment were negative. The spinal fluid of 14 patients reexamined 6 months after treatment were also negative.

Ten cases were followed for a period up to 6 months. In this group there occurred the only clinical relapse observed thus far 60 days after treatment. This patient suffered from sero-positive primary syphilis and was treated over a period of 5 days with single daily injections of penicillin in water-in-oil emulsion (900,000 Oxford units

the first day and 700,000 Oxford units daily for 4 days), simultaneously with a daily dose of 100,000 Oxford units in saline

Fourteen patients remain under observation for period of 6 to 10 months, none show any signs of clinical relapse, there are, however, 2 patients with persistent positive serologic reaction requiring further observation, and a third patient with secondary syphilis whose serologic test reversed from negative to positive 8 months after treatment

Injections of penicillin in the oily vehicle did not produce any serious side effects except transitory pains of varying intensity at the site of injection. Herxheimer reactions of a mild degree occurred in most cases

For purposes of comparison two patients were treated with corresponding single daily injections of penicillin (total dosages of 2,000,000 and 4,200,000 Oxford units) in saline alone both patients suffered clinical relapses within 2 and 3 months respectively

Comparison of penicillin serum and urine levels in patients receiving first a single injection of penicillin in saline and 5 days later a single injection of identical amounts

of penicillin in water-in-oil emulsions shows the following findings

1 No essential difference in the duration and height of penicillin serum levels was noticeable among the 2 groups

2 The 24-hour urine levels of patients who received single injections of penicillin in water-in-oil emulsion were twenty to one thousand fold higher than the urine levels of the patients after single injections of identical amounts of penicillin in water

3 These findings correlated with clinical results now indicate that the administration of penicillin in water in oil emulsion prolongs the therapeutic effect of the antibiotic agent within the body, even though assailable penicillin serum levels could not be detected consistently

Four patients received oral penicillin treatment. Of three receiving 6,000,000 Oxford units over a period of 6 to 10 days, 2 remain under observation. They are completely negative both clinically and serologically for a period up to 10 months. The fourth patient received a total dosage of 12,000,000 Oxford units over a period of 10 days, and displayed a clinical relapse after 65 days

\* \* \*

## Galactose Removal Constant

*In Expulsion of Galactose Disappearance From the Blood Stream Its Application As A Test For Liver Function*

HENRY COLCHER, ARTHUR J. PATEK, JR., AND FORREST E. KENDALL

The rate of disappearance of galactose from the blood stream after a rapid intravenous injection was studied in 64 patients with and without liver diseases. A 50 per cent galactose solution was injected intravenously in amounts corresponding to 0.5 gm per kilo body weight. Blood specimens were obtained before and at 15 minute intervals after the injection for a period of 90 minutes. Urine was collected as voided over a 4 hour period. The determination of blood galactose was based upon Benedict's method for blood sugar after removal of

glucose by fermentation according to the method of Raymond and Bianco

When the logarithm of blood galactose concentration is plotted against time a straight line is obtained. This straight line may be interpreted to indicate that the rate of removal of galactose from the blood is directly proportional to the concentration in the blood. By use of the following equation a constant,  $k$ , was calculated

$$k = \frac{2.3 (\log C_1 - \log C_2)}{t - t_1}$$



$C_1$  and  $C_2$  are the concentrations of blood galactose (in mg/100 cc) at times,  $t_1$  and  $t_2$ , expressed in minutes.  $K$  represents the fraction of the total amount of galactose present at any given time that is removed from the blood each minute. If  $K$  is multiplied by 100 the numerical value obtained expresses the percentage of the amount present that is removed each minute. This might be called the Galactose Removal Constant or GRC.

The Galactose Removal Constant can be calculated with sufficient accuracy from two blood specimens obtained at 15 and 45 minutes after intravenous injection. Under these conditions the constant may be calculated by the following equation:

$$\text{GRC} = 76 (\log \text{conc at 15 min} - \log \text{conc at 45 min})$$

The value of GRC varied between 42 and

95 in 10 controls and was below 4 in 43 patients with parenchymal liver damage (26 patients with cirrhosis of the liver, 7 cases of hepatitis and 10 patients with chronic passive congestion of the liver). In one patient with acute hepatitis the value of GRC was 19 and 194 on the 4th and 14th day of illness and returned to normal value of 62 three months after clinical recovery.

A series of determinations pertaining to liver functions were performed simultaneously with the galactose test on all patients. These included serum protein partitions, serum bilirubin, plasma prothrombin, cephalin cholesterol flocculation, bromsulphalein dye retention and urinary urobilinogen excretion. There was a good correlation between the values of galactose removal constant and other liver function tests.

## *The Etiologic Agent of Pemphigus Vulgaris\**

ARTHUR W. GRACE

### INTRODUCTION

In a search for additional data upon the etiologic agent of pemphigus vulgaris,<sup>1,2</sup> pathologic and control materials were inoculated into the brains of irradiated and normal mice.

### MATERIALS

The inocula consisted of

*A. Materials obtained from persons suffering from pemphigus vulgaris*

Twelve blisters arising spontaneously, 3 cantharides-induced blisters, 8 cerebrospinal fluids, 6 whole bloods, 1 blood plasma, 5 blood sera, 2 washed blood cells, 3 tissues obtained at autopsies.

*B. Materials obtained from persons suffering from diseases other than pemphigus vulgaris*

Three blisters arising spontaneously, 1 cantharides-induced blister.

*C. Materials obtained from normal persons*

Three cantharides-induced blisters, 2 blood sera.

*D. Materials obtained from mice*

Seventy-eight irradiated mouse brains containing heat-inactivated RP strain of virus, 15 irradiated normal mouse brains.

### RESULTS

Nine strains of non-bacterial agents transmissible to mice, were obtained from 7 persons suffering from pemphigus vulgaris. Four of the strains were derived from spontaneous blisters, 3 from cerebrospinal fluids and 2 from blood sera. No transmissible agents were obtained from any of the other materials. The strains were transmitted for the following number of passages respectively: 242, 11, 5, 4, 1, 1, 1, 1, 1. No attempt was made to transmit 3 of the ma-

\* From the New York Hospital and the Department of Medicine, Cornell University Medical College and the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine. Aided by grants from the John and Mary R. Markle Foundation and from the Dazian Foundation for Medical Research.

terials for more than 1 passage

The criterion of the presence of the agent was the appearance in the brains of infected mice of discrete and diffuse macroscopic and microscopic, collections of polymorphonuclear leukocytes. In some instances, the spinal cord and meninges were also involved in the same histologic change. Sick animals whose brains did not show this change were not regarded as having been infected.

Close study was made of the RP strain of virus, which was transmitted for 242 passages, with the following results:

a. The virus is unlike any spontaneous mouse virus hitherto described.

b. Neutralization experiments were performed with sera obtained from 10 normal persons and from 13 persons suffering from pemphigus vulgaris. Some degree of neutralization was obtained with some normal sera but definitely higher degrees of (and in one case, complete) neutralization were obtained with pemphigus sera. The serum from another case of pemphigus showed the development of a high degree of neutralization coincident with clinical remission and its disappearance in a relapse which terminated in the death of the patient.

c. Rabbits received virus by corneal scarification and by intradermal, intracerebral, intratesticular and intraperitoneal routes. Guinea pigs were inoculated sub-

cutaneously, intracerebrally and intraperitoneally. No pathologic changes were produced in the animals. The virus, therefore, was not that of herpes varicella, rabies, chorio meningitis or lymphogranuloma venereum.

d. No growth occurred in medium used for the growth of pleuropneumonia-like organisms.

e. Experiments in which an inoculum was employed whose concentration was 20 times that used for infection of irradiated mice showed that, while infection of non-irradiated mice occurred readily, it was impossible to maintain the virus for more than 3 or 4 passages in non-irradiated mice.

f. Vesicles accompanied with intense ectodermal, mesodermal and endodermal cellular reaction were produced by depositing the virus on the chorioallantoic membrane of the developing chick.

#### CONCLUSION

The data gathered in this study warrant the conclusion that the virus whose characteristics are outlined in this paper is the etiologic agent of pemphigus vulgaris.

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## Some Pharmacological and Clinical Experiences with Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl)

THOMAS H. MCGAVACK, HERBERT ELIAS AND LINN J. BOYD

The action of dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) was studied in 60 normal subjects and in more than 200 patients with various forms of allergic and other diseases in which sudden releases of histamine may play a pathogenic role.

The various systems of the body were systematically checked in the 'normal' subjects and in some of the patients for both physiological and toxic actions of the drug.

The data obtained has been correlated under three main headings: (1) physiological and pharmacological effects of the drug as observed in 'screening' tests for the functions of the various systems of the body in all of the 'normal' subjects and in some of the patients, (2) the therapeutic range of activity of benadryl, (3) the nature and frequency of toxic reactions.

1. *Effects of benadryl upon various bodily systems and functions.* The positive

data which were obtained in the study of 'normal' subjects and some of the patients indicated

a A depression of the secretion of gastric acid in 19 of 21 subjects studied, noticeable with doses of 150 mg daily, and occasionally reaching a state of complete suppression when 400 mg were administered daily

b A depression of the dermal response to histamine in all of 20 normal subjects and in 7 patients studied There was complete suppression of the response when patients were kept on from 300 to 400 mg of drug daily for several weeks Reactions to the injection of histamine were continuously abolished promptly by the intravenous administration of 20 mg of benadryl

c An atropine-like action of topically applied benadryl upon the pupil of the eye, maximal in degree by the end of 1 hour This was hastened not increased by epinephrine Benadryl increased the action of atropine and decreased that of eserine

d The development of orthostatic hypotension in approximately 8 per cent of all subjects studied

e A moderate decrease in the capillary permeability of subjects receiving doses of 300 to 400 mg of benadryl daily

2 *The therapeutic range of activity of benadryl* Benadryl proved to be most highly effective for the control of acute and chronic urticaria, angio-neurotic edema, allergic eczema, hay fever and vasomotor rhinitis Good but less reliable effects were observed in patients with bronchial asthma, neurodermatitis, dysmenorrhea and spastic colon

In many instances relief was afforded patients who suffered from Menière's syndrome, migraine, 'intractable' insomnia, a variety of gastrointestinal neuroses (other than spastic colon), and cardiac asthma However, the results do not warrant conclusive statements regarding the routine usefulness of the drug in these conditions A questionable influence upon essential hypertension and the tremor of paralysis agitans has been noted In several other conditions of widely diverse nature, no beneficial action could be demonstrated

3 *The nature and frequency of toxic reactions* Drowsiness was the most frequent and most distressing untoward manifestation of the action of benadryl It was usually most marked after the first dose or doses of the drug, later a 'tolerance' was commonly established A single dose of 50 mg has evoked a severe response, necessitating the use of coffee or benzedrine sulfate to keep the subject awake Other unpleasant symptoms in the order of their frequency included dizziness, blurring of vision, dryness of the mouth, and an "all gone feeling" at the pit of the stomach None of the reactions observed in any way endangered the subject's life or health, and all disappeared in from one-half to several hours after discontinuing the drug Moreover, as a rule the drug could be resumed without untoward effect by stepping up the dose gradually

It was concluded that benadryl is a powerful antihistamine agent which has in addition weaker but definite antispasmodic activity of an atropine-like type

## *The Clinical Evolution of Vascular Damage in Diabetes Mellitus*

HENRY DOLGER

The long recognized association of vascular damage with diabetes mellitus was emphasized in 1936 by Kimmelstiel and Wilson in a report on intercapillary glomerulosclerosis Our observations indicate that this triad of retinopathy, hypertension, and albuminuria is more than a terminal "pathological" syndrome

When diabetic patients, young and old, mild and severe, were scrutinized carefully over a period of years, such vascular damage was found in every instance When 200 patients below fifty years of age were followed diligently for 25 years, not one escaped retinal hemorrhages, albuminuria and/or hypertension in varying degree The

group investigated consisted of 16 whose age of onset of diabetes was below 10 years, 39 whose age of onset was between 10 and 20 years, 22 between 20 and 30 years, 43 between 30 and 40 years, and 80 between 40 and 50 years. There was no preexisting hypertension in any of these persons.

Retinal hemorrhage was the predominant lesion when diligent search was made routinely, and it often preceded the appearance of albuminuria and/or hypertension. When this sequence was not observed it could probably be attributed to failure to notice transient hemorrhages which had resolved in the interval between examinations. All three lesions appeared in the patients regardless of the age of onset or degree of severity of the diabetes, the need for insulin, the type of diabetic "control" or diet employed, the blood cholesterol levels, or the absence of any evidence of arterial calcification.

Careful repeated examinations of the eye grounds, blood pressure, and urine for albumin revealed no single instance where the diabetes had lasted 25 years in which the patient escaped the development of vascular damage. Some presented rapid progres-

sion into the full blown clinical syndrome of intercapillary glomerulosclerosis frequently with blindness. In the majority, however, the lesions progressed slowly with accelerated damage occasionally in isolated viscera and tissues such as renal, coronary and cerebral vessels, etc. The finding of specific renal vascular lesions on postmortem examination in 68 per cent of all diabetic patients was reported in 1944 by Laipply, Eitel and Dutra. This may now be considered a low estimate in view of our finding of vascular lesions in 100 per cent of all diabetics followed 25 years. In the middle age groups, the damage often appeared within 5 years of the onset of diabetes and not infrequently was noted coincidental with the onset. In a few instances, the lesion seemed to antedate the onset of clinically detectable diabetes.

Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit of insulin in prolonging life. At most, 25 years of freedom from arteriosclerosis can be offered even to the juvenile diabetic. The prevention of these inevitable sequelae are a challenge to the future.

### *Insulin Resistance: A Case Study*

THOMAS H. MCGAVACK, SOLOMON D. KLOTZ, MILDRED VOGEL and  
JAMES F. HART

A 64-year old man with diabetes of 7 years duration has been observed in 3 periods of "insulin resistance" with severe ketonuria and glycosuria, during which a "peak" daily dose of insulin has been 3250, 1320 (100 intravenously), and 500 units respectively. Between these periods the patient's urine has been free of sugar and acetone without exogenous insulin. During the third period of resistance, the presence of allergic antibodies has been demonstrated repeatedly by the use of the Kustner-Prausnitz method for the passive transfer of sensitivity. Such reactions disappeared within 10 weeks after insulin was discontinued and reappeared within 10 days after its resumption.

Other protective substances of a directly

anti-insulin or anti-hypoglycemic nature were sought for in the blood of the patient. However, repeated tests failed to show that his blood was capable of protecting mice from otherwise fatal doses of insulin.

Following an acute pancreatitis associated with the formation of a pseudo-cyst, the patient's sensitivity to insulin has become normal, and the allergic reactions previously noted can no longer be demonstrated.

It is concluded that under certain circumstances insulin may act as an allergen, the development of antibodies may be so great that severe resistance to the action of insulin results. The data are discussed in relation to previous concepts of insulin resistance as revealed in the literature.

## *Experiences with Folic Acid in Macrocytic Anemia*

LEO M MEYER

Data are presented concerning the use of folic acid in the treatment of 7 cases of pernicious anemia. Three of the patients received folic acid in doses of 50 mg orally or 20 mg intramuscularly daily. Clinical improvement with relief of symptoms and increases in hemoglobin, red cells and reticulocytes followed. However, complete hematological remissions could not be obtained, and 2 of the patients showed progression of their neurological signs and symptoms. The third died on the 37th day of bronchopneumonia. Four other patients were treated with combinations of 5 or 10 mg of folic acid plus  $\frac{1}{2}$  unit of liver extract intramuscularly, daily. On this regime

symptoms were relieved and blood pictures became normal. Reticulocytes rose to levels greater than those anticipated with liver alone and 2 of the patients with neurological signs were distinctly improved.

The author concludes that folic acid, by itself, fails to raise the Hb and red cells to normal levels and is unable to prevent the development or progression of signs of subacute combined sclerosis. However, the combination folic acid and small doses of liver produces a more rapid rise in the Hb and RBC with higher reticulocytosis and is effective in preventing and curing involvement of the central nervous system.

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## *A Study of Histochemically Demonstrable Liver Phosphatase in Experimental Obstructive Jaundice and in Human Postmortem Material\**

M WACHSTEIN and F G ZAK

Methods capable of demonstrating enzymatic reactions in tissue sections have opened a new approach to the study of various biological problems. In view of the marked changes in serum alkaline phosphatase activity occurring in liver disease, a study of this enzyme in liver sections under experimental conditions, as well as in postmortem material, was undertaken. Gomori's method, as modified by Kibat and Furth with some minor alterations was used.

Little stainable phosphatase was present in the livers of normal rats and mice. Increase in cytoplasmic alkaline phosphatase activity in the atrophic liver cells of starved, in the hydropic liver cells of protein depleted mice, and to a lesser degree of rats, has been described in a previous paper (*Arch Path* 1945, 40,57). In the livers of animals poisoned by phosphorus, chloroform

and carbon-tetrachloride there was no significant increase of phosphatase in necrotic cells.

In continuation of these experiments the common bile duct was ligated in 9 dogs after an initial biopsy had been taken. In the dog liver the bile capillaries showed conspicuous phosphatase activity. After the ligation there occurred a marked rise in serum alkaline phosphatase as described by various investigators. There was marked dilatation of the bile capillaries, increasing with the duration of the experiment. This widening apparently was caused by the accumulation of phosphatase in the liver cells around these structures. Considerable dilatation of bile capillaries was also seen in the livers of several rabbits 4 to 5 days after the ligation of the common bile duct.

The postmortem material included both

\* From the Laboratories of the E. A. Horton Memorial Hospital, Middletown, New York, and Mt Sinai Hospital, New York.

sections from livers not involved by disease, and sections from livers which had been the seat of various pathological processes. In liver sections from patients whose death was due to various causes and in which no significant gross or microscopic changes were found, only little alkaline phosphatase activity was demonstrable in the liver cells, while the sinusoids, as well as the bile capillaries, showed a varying degree of activity. In 8 cases of obstructive jaundice there was dilatation of bile capillaries which, however, was absent in the 2 remaining instances. The degree and extent of the widening of the bile capillaries as seen in these preparations stained for alkaline phosphatase activity varied considerably. It was only focal in some and fairly uniform in others. Necrotic liver cells in these livers as well as in a number of other livers in which extensive necrosis had occurred, did not show increase in enzymatic activity. In a case of subacute yellow atrophy and in a case of toxic (post-necrotic) cirrhosis, there was conspicuous activity in the proliferating connective tissue and the infiltrating round cells. Marked staining of the connective tissue occurred also in some cases of Laennec cirrhosis while in other cases, obviously in a more quiescent stage, the connective tissue showed only little activity. In several cases in which hepato-cellular changes were superimposed and in which jaundice as well as

increase in serum alkaline phosphatase had been present, focal dilatation of bile capillaries was seen while otherwise the liver cells did not show any alteration in their enzymatic activity. In several livers of patients who died from various causes (cardiac failure, glomerulo-nephritis, etc.) but without clinical and anatomical evidence of significant liver disease, considerable increase in cytoplasmic alkaline phosphatase activity was found.

The origin of the increased serum alkaline phosphatase in liver damage is still controversial. The behavior of histochemically demonstrable phosphatase activity in the liver under experimental conditions and in human postmortem material favors the assumption that this rise is due not to increased production in the diseased liver, but rather to the inability of the liver cells to excrete the enzyme. This may be caused either by external obstruction, or by cellular dysfunction. The blood level of alkaline phosphatase probably is in addition influenced by extra-hepatic factors, since phosphatase can be excreted in the pancreatic juice and through the intestinal tract and in addition through the kidneys in some species. Disturbances in calcium and phosphor metabolism in hepatic disease may influence the production of this enzyme in the osseous system.

## LIBRARY NOTES

THE "HERNIA CONGENITA" AND AN ACCOUNT OF THE CONTROVERSY  
IT PROVOKED BETWEEN WILLIAM HUNTER AND PERCIVALL POTT\*

FENWICK BEEKMAN

PERHAPS it may be as sound philosophy to say, that all the actions of men are directed to some good end, as it is to subscribe to an opinion which has prevailed among naturalists, that, in the works of nature, nothing is absolutely without its use. Literary disputes are disagreeable to the greatest part of mankind, and the disputants are, for the most part, condemned by the world. Yet it is reasonable to think, that even these disputes answer some good purpose. By engaging the passions of men more warmly, they rouse a spirit of emulation, and give a spur to enquiry.

"It is remarkable, that there is scarce a considerable character in anatomy, that is not connected with some warm controversy. Anatomists have ever been engaged in contention. And indeed, if a man has not such a degree of enthusiasm, and love of the art, as will make him impatient of unreasonable opposition, and of encroachments upon his discoveries and his reputation, he will hardly become considerable in anatomy, or in any other branch of natural Knowledge.

"These reflections afford some comfort to me, who unfortunately have been already engaged in two public disputes" (Hunter, Wm—*A Supplement to the First Part of Medical Commentaries*, p. iii.) So writes William Hunter in *The Introduction* to his accusation of plagiarism against Percivall Pott. At the time he brought this charge against his friend and fellow practitioner he was but concluding long and heated controversies over priorities in anatomical discoveries with his former teacher and friend, the venerable Alexander Monro of Edinburgh, for whose learning he held great respect. But in William Hunt-

\* The biographers of both William Hunter and Percivall Pott have written little of this dispute merely mentioning its occurrence.

er's opinion, the establishment of justice in anatomical discoveries, by placing credit where he thought it belonged, surmounted all other considerations, whether they were ties of friendship, blood relationship, or the veneration for an old master. He writes "A Controversy relating to any improvement or discovery in the arts, when there are complaints of unfair dealing, is an awkward [sic] subject for a party principally concerned. The writer must plead his own cause, and where he thinks himself in the right, and ill-treated, he will be led to speak in his own favour, and to the prejudice of another person, both which a man of an ingenuous turn of mind would willingly avoid" (Hunter, Wm—*Medical Commentaries*, p. v.) Continuing, he informs us that a writer in such a dispute may appear to magnify trifles and be looked down upon as a petty person. And finally he writes

"Another circumstance, as unpleasant as either of those already mentioned, is, that in order to do justice to the cause, it may be necessary to say many things, which an author would wish to avoid, he may be obliged either to suppress his evidence, or to call upon his friends, and publish matter of private conversation, in short, to mention many things, which though, for some reason or other, it may be disagreeable to relate them, are yet necessary in the defence of truth" (*ibid*.)

With these opinions of William Hunter before us, we may now take up the story of a particular controversy, between him and Percival Pott.

During the winter of 1755-56, John Hunter is found busily investigating the descent of the testis in the foetus during the late months of intra-uterine gestation. This subject had been first brought to the attention of his brother, during the year 1748, by Samuel Sharp, who enquired of William Hunter whether when "dissecting ruptures" he "had ever found the intestine in the same bag, and in contact with the testis" (Hunter, Wm—*Medical Commentaries*, p. 70.) A few weeks later a body of a man with bilateral hernia having come under William Hunter's observation, he called Mr. Sharp and together they dissected out these ruptures, "as soon as the hernial sac of the right side was laid open," writes William Hunter, "we saw the *testis* lying bare, in the bottom of its cavity—Then we dissected the rupture of the left side, and there it was as indisputable that the bottom of the hernial sac was situated upon the outside of the *tunica vaginalis propria* or, in



other words, that these two bags were distinct and without any communication, and that the intestine in such a rupture could not have come in contact with the *testis*, unless a laceration had been produced both in the hernial sac, and in the *tunica vaginalis propria*. We therefore concluded that such a laceration of those bags had actually happened to the rupture on the right side, and that it must happen in all ruptures where the *testis* is found in contact with the intestine" (*ibid* p 71). So sure was Sharp that a congenital hernia (the name by which it is known today) was actually due to a rupture or laceration of a simple hernia sac into that of the tunica vaginalis, that he wrote, two years later, "it is evident to me that notwithstanding the *Peritoneum* may at first fall down with the *Viscera*, yet in length of time it may also be ruptur'd, because I have found the *Intestine* and *Omentum* within the *Tunica Vaginalis* of the Testicle, and in contact with the Testicle itself, which they could not possibly have been, if they were envelop'd in a portion of the *Peritoneum*. However this Circumstance occurs but rarely, for we usually find the *Viscera* within a *Prolapsus* of the *Peritoneum*, which Prolapsus is now known by the Name of the *Hernary Sack*" (Sharp, Samuel—*A Critical Enquiry*, etc., p 3).

The Hunters did nothing further to unravel the mystery surrounding the cause of oblique inguinal hernia until late in the year 1755 soon after William had read Albrecht von Haller's observations on the *hernia congenita*, which appeared in the newly published *Opuscula Pathologica*. From this communication he learned much that was new to him concerning the subject. Some of Haller's opinions were, that in the foetus the testicles are "lodged in the cellular membrane of the loins, contiguous to the kidneys" "The descent of the testicles is gradual, and after some time, which has not hitherto been determined, they fall down into the Scrotum, always behind the Peritoneum, as now they are situated under it. The cause of this progression seems to be owing to the force of respiration, and the action of the abdominal muscles" (From this it appears that Haller believed the descent of the testicles occurred after birth.) And finally William Hunter learned of Haller's opinion concerning the development of a hernia following the descent of the testicle, as given below:

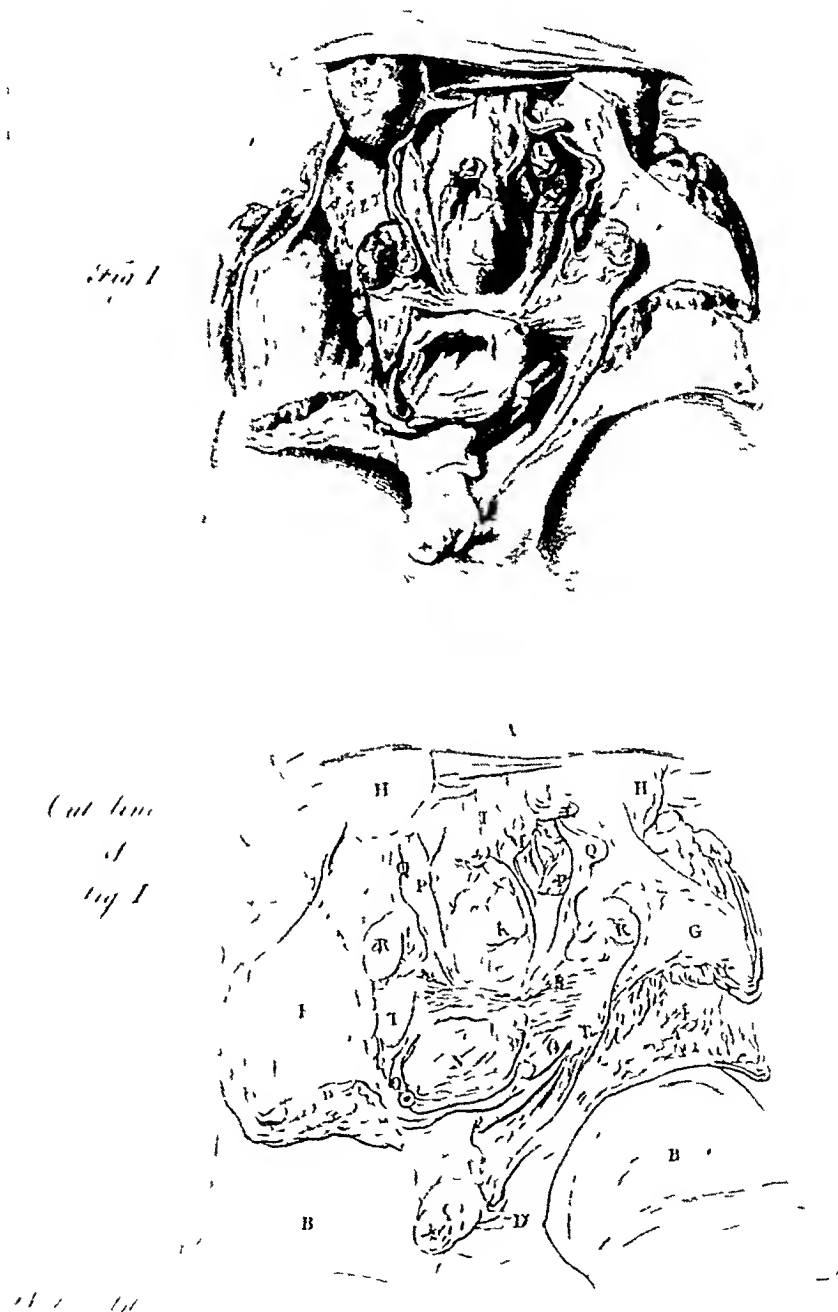
"Hence, if I am not mistaken, the manner how congenial Hernias are formed, very plain appears. The process of the Peritoneum under the kidneys is open, in order to receive the testicle,

and that being pressed downwards, as usual, the testicle at the same time is carried along with it, and both together fall down into the Scrotum But as in these bodies the testicles are contained in one and the same bag with the intestines, it is not at all singular or surprizing that a slight impulse should force down the latter into this open space”\* (Haller, Albert—*Pathological Observations*, p 59)

Speaking of this newly acquired knowledge in later years William Hunter said “it struck my imagination that the state of the *testis* in the *foetus* and its descent from the *abdomen* into the *scrotum* would explain several things concerning ruptures and the *hydrocele*, and particularly that observation which Mr Sharp had communicated to me, viz, that in ruptures the intestine is sometimes in contact with the *testis*” (Hunter, Wm—*Medical Commentaries*, p 72) Having communicated his thoughts to his brother, John had then begun an investigation to ascertain “the state of the *testis* before and after birth, and the state of ruptures in children” (*ibid*) John Hunter was not, however, entirely ignorant of this subject, as his brother informs us that “Several years before Haller’s *Opuscula Pathologica* were published, my brother informed me, that in examining the contents of the abdomen of a child, still born, about the seventh or eighth month, he found both the testicles lying in that cavity, and mentioned the circumstances with some degree of surprise” (Hunter, John—*Observations on Certain Parts of the Animal Oeconomy*, p 1) During this winter (1755-1756), John Hunter prepared a number of specimens to demonstrate the stages in the descent of the testis, from dissections made upon foetuses of different ages\*\* From these specimens, the artist, I V Riemsdyk, made numerous drawings, from which three plates were finally prepared that later were used as illustrations for John Hunter’s paper, that first appeared in William Hunter’s *Medical Commentaries* during the year 1762, with the title of “Observations on the State of the Testis in the

\* Sir Richard Owen writes that Although Haller was in doubt as to the exact period of the descent of the testis and in error as to the cause of that phenomenon yet he accurately describes in the original paper here alluded to the original relations of the gland to the peritoneum and abdominal viscera, and the formation of the tunica vaginalis and thus applies the facts which he had discovered to the explanation of the disease he was considering (*The Works of John Hunter* Edited by Jas F Palmer Vol IV p 2 fn)

There are eight specimens illustrating the descent of the testis in the Hunterian anatomical museum of the University of Glasgow John H Teacher in the Catalogue of the Anatomical and Pathological Preparations of Dr William Hunter in the Hunterian Museum, University of Glasgow, Vol II p 58 writes The specimens [42-60] from which Plate I was taken were readily identified but as to that (or those) from which Plates II and III were drawn there is some doubt there being none which correspond exactly The visitor to Glasgow is well repaid if he seeks out these specimens (see illustration) which are not only of historical interest but may still be studied with value from an anatomical standpoint



"Fig 1" from John Hunter's *Observations on the State of the Testis in the Foetus, and on the Hernia Congenita* Representing "the testes within the abdomen, in an abortive foetus of about six months"

Foetus and in the Hernia Congenita", and later was republished, with only minor additions, in the year 1786, in John Hunter's *Observations on Certain Parts of the Animal Oeconomy*, under the heading of "A Description of the Situation of the Testis in the Foetus, with its Descent into the Scrotum"

This description of the descent of the testis, together with explanations for the cause of abnormalities that occasionally occur, as portrayed by John Hunter in this article, his first written presentation, is given most accurately in anatomical detail, in which particular stress is paid to the blood supply. With the exception of a few additional facts that have been only recently discovered, this work still stands as authority. Besides the anatomical facts, he describes, most minutely, each step occurring during the progress of descent, showing the manner in which the testicle carries a pouch of peritoneum before it and how the distal portion of this pouch normally isolates itself from the peritoneal cavity, in order to form the tunica vaginalis. The descent, he informs us, occurs before the time of birth (a statement in which he differs from Haller) and he writes

"From this original situation within the *abdomen* the *testis* is afterwards moved to its destined station in the *scrotum*. It is the more difficult to ascertain the exact time of this motion, as we hardly ever know the exact age of our subject. According to the observations which I have made it seems to happen sooner in some instances than in others, but generally about the eighth month. In the seventh month I have commonly found the *testis* in the *abdomen*, and in the ninth I have as commonly found it in the upper part of the *scrotum*" (Hunter, William—*Medical Commentaries*, p 80)

He also shows that if the distal portion of this peritoneal pouch is not isolated, a congenital hernia sac or an infantile hydrocele persists. He mentions further that a fixed portion of the intestine might occasionally be drawn down into the scrotum as a part of the wall of the pouch of peritoneum (a condition which today we know as a sliding hernia). Finally, he differentiates between the non-descent of the testis and a displaced testis. In this part of his paper he lays down several important suppositions concerning non-descent of the testicle, which have as yet not been disproved. "It is not easy to ascertain the cause of this failure in the descent of the testicle", he writes, "but I am inclined to suspect

that the fault originates in the testicles themselves' (Hunter I—*Animal Oeconomy*, p 15) "When both testicles remain through life in the belly, I believe that they are exceedingly imperfect, and incapable of performing the natural functions of those organs, and this imperfection prevents the disposition for their descent taking place" (*ibid*—p 18)

William Hunter informs us that six years before the publication of *Medical Commentaries*, in April 1756 when he was concluding his lectures for the season with a course on "the chirurgical operations, I gave a very general account of my brother's observations, and shewed both the drawings of Fig II which was then finished, and the subject from which it was made" (*Medical Commentaries*, p 72) Because of this demonstration before his class, William Hunter assumed, it seems, that he had established his right to priority for describing the *hernia congenita*. No wonder he was both surprised and irritated, during the following June or July, to receive from his friend, Percivall Pott, a copy of the latter's book, *A Treatise on Ruptures*, in which he found a discussion of the *hernia congenita*, without credit being given to either himself or his brother for their investigations upon this subject.

"In the preface I found that he had done me the honour of adding my name to a very respectable list [William Hunter indignantly writes], and I imagined that this compliment was meant as a very kind return for the respect which I had wished to shew him upon every occasion, and particularly for what had passed between us some time before, at a meeting for examining the nature of ruptures, and the state of the parts concerned for when he began to compose his treatise (as I presume, because though he said nothing to me of such an intention, I soon after heard of it among his friends) he desired that we might examine those things in the first proper subject which I could apply to that purpose" (*ibid*—p 73)

At this meeting, William Hunter tells us, he demonstrated his ideas to Pott upon a body on which his brother, John, was at that time dissecting. The date of this meeting I think must have been immediately preceding the middle of January 1756, for about that time Percivall Pott was thrown from his horse sustaining a compound fracture of the leg. "During the leisure of his necessary confinement" from this injury, Pott's son-in-law tells us, "he planned, and partly executed his

treatise upon ruptures, which was completed by the latter end of the year (Earle, Sir James—*A Short Account of the Life of Mr Pott*, p 11)

The appearance of a new publication by Pott in March 1757, entitled *An Account of a Particular Kind of Rupture Frequently attendant upon New-Born Children*, did much to make matters worse, and precipitated a disgraceful altercation between the two men. In this treatise of forty-one pages, Pott presents his views upon the *hernia congenita* without even mentioning the Hunters.

A review of this book, appearing in the *Critical Review* of March 1757, in all probability written by William Hunter's friend Tobias Smollet, insinuates that Pott had borrowed the material for his work from Haller and the Hunters. Referring to these accusations, the reviewer writes

"He [Mr Pott] quotes Mr *Cheselden* and Mr *Sharp*, and himself in his last years production upon ruptures, to shew that though the facts had been known, yet the theory, or true cause of the contiguity of the gut and testicle had not been understood, but he does not tell us that Dr *Haller*, in his *Opuscula Pathologica* (which we gave an account of last year) has anticipated this discovery, in the account he gives of the congenital rupture. He has likewise the misfortune to be under suspicion of having learned all that he has published upon this subject at second hand, and imperfectly from Dr *Hunter's* lectures. We are informed, by a letter from one that calls himself a pupil of Dr *Hunter*, that this celebrated anatomist has in his three last courses explained fully everything in Mr Pott's book, that he shewed, at his lectures not only preparations of the parts, but drawings of them which his brother had provided, in order, with proper opportunity, to publish the observations which he had made upon this subject. This pupil further adds, that Dr *Hunter* complained of Mr *Pott's* publication, and appealed to many gentlemen as well as to Mr *Pott* himself, that he had above a twelve month ago made no secret of the discovery.

In appealing to Percivall Pott "to clear up these disagreeable appearances", Hunter presents his view on this accusation of plagiarism as follows

'In my autumn course of lectures 1756, (and indeed in every

course, which I have read since that time) I demonstrated the principal things contained in my brother's account of the *testes* in the *foetus*, and I particularly explained that species of rupture in which the intestine is found in contact with the *testis*. This circumstance of the disease, which had puzzled Mr Sharp and Mr Cheselden as well as myself, and which even Mr Pott regarded as a *lusus naturæ* [an accident], was now rendered perfectly intelligible. The discovery was become the novelty of the time among students in London, and other inquirers after anatomical improvements, and many gentlemen of my acquaintance desired to see the preparations which my brother had made, and among the rest my friend Mr Pott did us that honour, one day during that course of lectures I was not present. My brother shewed him the preparations with great readiness, and explained to him my hypothesis of the contiguity of the intestine and *testis* in some ruptures. Mr Pott said nothing at that time of an intention to write upon the subject, but, some weeks afterwards, it appeared, by a public advertisement, that he was soon to publish a treatise on that species of rupture. I was much surprized, however, I thought it proper to say but little, till I should see how he treated the subject. The treatise came out in the month of March, 1757.—It hardly contained one new idea. It was what any of my pupils might have written, (for the cases given in the end supported only an uncontested fact) and yet neither my brother's name, nor mine was mentioned. It bore strong marks of *secondhand* observation, and of a *time-serving* hurry in the composition" (Hunter, Wm—*Medical Commentaries*, p 89.)

Percivall Pott's defense to these charges, made against him in the article appearing in the *Critical Review* for March 1757 and by William Hunter in *Medical Commentaries* published in 1762, was not long forthcoming, for in October, 1763, a second edition of *A Treatise on Ruptures* came off the press. This contained a chapter giving an account of his side of the dispute. It is creditable to Pott that he shows so little rancor against his vilifiers, for he merely makes simple denial of all the charges. His language, in fact, is so restrained that it aroused a spirit of justice within William Hunter, so much so that he wrote "He has treated me, for the most part, with the language of a gentleman, for which I thank him. I have indeed, received some *incision* at his hand

but little *butchery*, and I have been so much used to meet with the latter, that I am the more sensible of his legitimacy" (Hunter, Wm—*A Supplement to the First Part of Medical Commentaries*, p v )

Before starting upon the arguments for his defense, Pott apologizes to his readers for entering the dispute, which was, it seems, most distasteful to him, by writing as follows

"I am perfectly sensible of how very little importance all these disputes are to all other people except the disputants themselves, and how very difficult it is for any man to tell what relates merely to himself, in such manner as not to tire and disgust those who have no interest in it, but as I have been (to use Dr Hunter's own words) *wantonly*, and I cannot help thinking malevolently attacked, and treated in a manner which appears to me highly ungenerous, not to say illiberal, I hope the reader will indulge me in the opportunity which this chapter affords of relating the facts, lest my silence should be misconstrued into an acknowledgement of the truth of what the doctor has said"

(Pott, P—*A Treatise on Ruptures*, 2d ed, p 139 )

Then, following an explanation of the manner in which (through investigations upon foetuses and stillborn infants) he had reached his opinions concerning the *hernia congenita*, the author launches upon his defense

The account which he gives of his visit to Dr Hunter's dissecting room, at the time when John Hunter received him, is much the same in general as that of Dr Hunter, but his version of the details of the discussion that took place is altogether different. Concerning this visit, Pott writes as follows

"Having always entertained a high opinion of Dr Hunter's *anatomical* abilities, I called at his house designing to have told him what I had done, and to have had some conversation with him on the subject. The doctor was not at home, but his brother Mr Hunter was, and with him I had some talk. The same gentleman also shewed me *one single preparation, tied down, in a glass, in spirit*, exhibiting the situation of the testicles of a foetus pretty near the time of their passing from the abdomen into the scrotum of which kind I had then several at home, and which many of my friends had seen. Mr Hunter did not show me any other preparation of any kind whatever, nor do I remember that the



congenial hernia was once mentioned by either of us during my short visit, notwithstanding the doctor has said that his brother "showed me his preparations with great readiness, and explained to me his (the doctor's) hypothesis of the contiguity of the intestine and testicle" Our conversation turned intirely on the passage of the testis from the belly into the scrotum, and as far as I could perceive (for he spake with the most cautious, apprehensive reservedness) our sentiments were alike "

My papers were at this time finished and corrected for the press, , nor did I alter a single syllable in them, in consequence of this visit to Mr Hunter (*ibid* —p 145 )

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This is a short and true account of the fact, this is the thing for which I have been traduced in print, as a plagiarist, and for which Dr Hunter has taken a liberty with me, which he can have no right to take (*ibid* —p 147 )

To the charge that "Mr P borrowed a remarkable paragraph from Baron Haller [that in which it is said the testicle descended after birth caused by the movements of respiration], and gave it to the world as his own in the first edition of his general Treatise on Ruptures', (Hunter, Wm—*A Supplement etc* , p 6) Mr Pott replies "I do aver that I never had seen, read, or heard of the book , till some time after the publication of my pamphlet on that subject I therefore did not, nor could borrow any part of the contents, either of that, or of my former treatise, from it the manner in which I attained my knowledge [by personal investigations] I have already most faithfully related, and therefore think myself intitled to the reader's credit But setting aside whatever pretension I may have to be believed upon my bare assertion, is it probable that if I had stolen my opinion from the baron's book that I should have given so short, so imperfect, and indeed so erroneous an account of what he has so fully explained, or at least so clearly pointed out?" (Pott, P—*A Treatise on Ruptures*, 2d ed , p 149 )

To the statement made by William Hunter that "It was what any of my pupils might have written," Pott retorts

"I do indeed most sincerely wish that some one of the doctor's pupils had prevented me from being engaged in this affair by having published what, *he says, they all knew*, to which he

might have added, *and they only*, for the rest of the medical world were so totally unacquainted with the subject, that mean and trite as my performance was, I received the thanks of many, I might say most of the practitioners of eminence, both in physick and surgery, for it They acknowledged themselves pleased and informed, and thought that it furnished them with a new idea, and what is more, do still continue to think so, notwithstanding the doctor's assertion " (*ibid* —p 153 )

Having spoken his mind and presented his defense, Percivall Pott concludes his remarks by "closing the door" to further part in this controversy, by writing as follows \*

"As I did neither *wantonly seek* this dispute, nor begin it, so now having said all that I know, or think concerning it, I am determined never to write another word on the subject, I therefore take my leave of it for ever, assuring both Dr Hunter and his brother, that when I published my tract on the congenial hernia, I had no intention to anticipate either of them, or to prevent either of them from enjoying any reputation, or honour, which might arise to them from their labours on this, or any other subject, on the contrary, when I presented my first treatise to the doctor, if he had been so friendly as to have hinted to me his suspicion of my having borrowed from Haller, or to have said, that he, or his brother, was then inquiring into that part of the animal oeconomy, I would not only have given him a true answer to the former, but should most probably never have prosecuted my inquiries into the latter, as I should have thereby known that the subject was in so able hands I wanted no reputation of that sort, but as I thought that I had accidentally hit upon a truth in which mankind were not a little interested, so I thought it my duty to publish it If my account was erroneous, it certainly deserved correction, but that correction might have been made with civility and candor, not in the manner in which the doctor, or his *nameless* pupil attempted it, if I had then been displeased, the fault would have been mine, and no blame could have justly been laid on the corrector The man who is offended by a civil offer of information, has more vanity than sense, but

\* Pott lived up to his word for he never again referred to this dispute and in the third edition of *A Treatise on Ruptures* published in 1769 Section V *The Congenial Hernia* contains not a single word concerning the controversy

he who tacitly and tamely submits to an attempt towards rendering him contemptible (by whomsoever made) does thereby become so" (*ibid* —p 162 )

The controversy did not, however, end here, as William Hunter could not, it seems, allow Percivall Pott to have the last word. Hence we find the former writing "I read it [Pott's defense], and found that we differ very widely in stating the facts upon which the whole dispute between us depends" (Hunter, Wm—*A Supplement, etc* , p iv ) "Yet, now that I have got all the light which he has given me, when I read over both accounts, and compared them together, I am still conscious that mine is exactly true in every particular, and that in his there are such mistakes and inaccuracies, as could not be expected from a man of his understanding and abilities, whether one considers him as a surgeon, or as an author" (*ibid* ) William Hunter felt in duty bound, it seems, in "justice to the public," as he says, as well as to himself, "to clear up the matter" by proving the truth of his accusations. This he attempts to do in *A Supplement to the First Part of Medical Commentaries* (1764), which was published in the year following the appearance of Pott's defense. The treatise contains a most detailed account of the dispute, but presents no new evidence against Pott. The text merely reiterates the charges Hunter had made and attempts to refute Pott's arguments by an analysis of his statements and the furnishing of copies of affidavits from students and practitioners to substantiate his claims. The whole treatise seems to be as uncalled for as it is undignified, in its cruel denunciation of a friend and fellow practitioner on insufficient evidence. The veracity of a man of standing in the community is willfully attacked and he is openly accused of plagiarism and denounced as a prevaricator.

It is not out of place, I think, in concluding this account, to add a few remarks upon the events that led up to the dispute and to analyze the claims put forward by the contestants in this unhappy controversy.

The credit for recognizing the relationship of the testicle to the hernia sac, in the congenital type of oblique inguinal hernia, must be given to Samuel Sharp, who, as we have seen, described the anatomical findings, but failed to identify its cause as being the result of a lack of embryological development.

There is no question that Albrecht von Haller was the first to demonstrate the relationship of the congenital hernia to the descent of

the testicle, the progress of which he describes with accuracy except for the time of its occurrence William Hunter quite fairly acknowledges all of this in *Medical Commentaries*

It is true that there is much to be found in Percival Pott's two treatises that might make one believe that he had read Haller's article before publishing *A Treatise on Ruptures* in the year 1756, for he adds nothing new and continues the false conception that the testicle descends after birth Pott, however, was, even at this time, the leading surgeon of London and known for his honesty and ethical standing in the profession We must, in consequence, I believe, accept his word that he had not known of Haller's article when preparing his treatise Against this statement, William Hunter puts forth much wordy argument, in which, though he produces no evidence to prove that Pott had borrowed information from Haller, he, nevertheless, points out the similarity of Pott's account of the descent of the testicle and his description of the *congenial hernia*, as he called it, to that given by Haller On this circumstantial evidence William Hunter attempts to convict his friend on the first charge of plagiarism

The second charge, that Pott borrowed information to be used by him, from the Hunters, can be, I think, as easily disposed of Both of Pott's treatises on the *congenial hernia* were published, as has been noted, some years before the appearance of John Hunter's article on the *hernia congenita* However, William Hunter assumed that he had established priority on this subject for himself and his brother, because he had included some remarks on their observations, concerning the descent of the testicle and the *hernia congenita*, in his lectures during the autumn of 1756 He further claimed, that he and his brother had both discussed this matter in detail with Pott at about the same time Pott, though he readily acknowledged the meetings, denied the detailed discussion of this matter, in fact he writes that John Hunter "spoke with the most cautious apprehensive reservedness" Comparing the subject matter of Pott's treatises with that contained in John Hunter's article, one is at once impressed with the superior knowledge of the subject, as laid down by the latter, and seeks in vain throughout the former's treatise, without finding the least suspicion that its author had used information that might have been acquired from William Hunter's lectures or through the discussions Pott had had with the brothers John Hunter, on the other hand, presents a detailed account of his

painstaking investigation, the observations he made and the conclusions he drew, in a scientific discussion which gives much information that is new and corrects statements of others that were false. All of this has stood the test of time.

From the facts presented, one suspects that, in the first place, William Hunter's claim to priority for discovery in this instance rests upon an insecure foundation and, second, his case against Pott lacks sufficient evidence of proof. If this is so, why, may we ask, did he make so public a matter of the controversy? Perhaps it was a sense of disappointment and frustration on his part, at learning of the publication of the article on *congenial hernia*, by Pott, when he and his brother were just about to conclude their extensive and painstaking inquiry into the same subject. He may have felt, it seems, that their work had been done in vain, though he should have realized that Pott's account was poorer and less extensive than theirs, where almost every statement was backed by observed facts. William Hunter, however, possessed great pride in his reputation and, as we have seen, an inordinate sense of justice, and being jealous, appears to have thought he should defend himself, especially since his old antagonist in Edinburgh, Alexander Monro *primus*, had chided him for quarreling with Pott.

In ending, it might be added that, though today such a publicly conducted controversy over a private matter would be considered vulgar and uncalled for, this was not the case during the eighteenth century in England, when such disputes, with charges and counter-charges, were commonly aired in the public press.

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GENERAL PATHOLOGY OF  
TUMORS OF ENDOCRINE GLANDS

*The First James Ewing Memorial Lecture\**

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THE notices which appeared in many scientific journals both here and abroad after the death of James Ewing make it unnecessary to itemize at this time his many accomplishments and the high honors bestowed on him. Nevertheless I cannot refrain from recounting some of my personal recollections. My acquaintance goes back to 1908, my friendship to 1911 and my devoted affection to 1918, dates which I consider noteworthy in my professional life.

Among many other tributes, James Ewing is the only man twice elected to the Council of the American Association of Pathologists and Bacteriologists. During the 14 years of that service, my post as secretary gave me the great privilege of close association with him and I was repeatedly a witness to a fine intellect at work on professional and administrative problems. Determined in learning basic facts, keen in analysis of them and logical in arrival at conclusions, he expressed himself

\* Delivered at The New York Academy of Medicine, May 2, 1946.

From the Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland.



with critical directness and conciseness, an example recalled with lasting admiration

On many occasions I enjoyed and benefited by his hospitality, especially at the Memorial Hospital. No visit to New York was complete unless I had his aid in histopathological diagnosis, nor was I satisfied unless I had the opportunity to learn of advances in oncology presented with his background of great experience and profound wisdom. Without entering into details, I must say that I am proud of numerous kindnesses at his hands, proud that a great man would think well of me, proud that I had something to do with one of the honorary degrees conferred on him, and proud of his loyal friendship. His undaunted courage and distinguished achievements in the face of physical handicaps and personal tragedies, his utter devotion to his profession, his power of persuasion, his critical judgment, his ideals, his humor, his modesty, his integrity of character and his wholehearted humanness must always be an inspiration.

Never given to publication for its own sake and impatient with "pot-boilers," Ewing's interest in the dissemination of knowledge was continuous. He was by nature a teacher imbued with the belief that what he learned was well worth passing on to others. This was shown in the deep understanding and clarity so evident in his book and in his numerous papers. Although he never sought personal acclaim, he would have been much gratified by the establishment of a Memorial by his friends and admirers. Education and the improvement of knowledge by research were close to his heart. In my opinion, he would have been especially pleased by the allocation to a lectureship of part of the funds which have been contributed, regardless of whether the lectures are in the field in which he attained fame or in other branches of science. He himself took pleasure in the instruction of students, assistants and associates and he had that greatest of attributes of a teacher, enthusiasm. His name will be perpetuated by his work, but the lectures will refresh the stimulus so well provided by his life and career.

It is utterly impossible to express the sense of honor I feel in my selection to deliver the first of these memorial lectures. I am touched to the heart by this distinction because of my admiration and affection for James Ewing and because of my lasting gratitude to him. My contributions to the field of oncology are insignificant, but over the course of twenty years I have had an exceptional opportunity to learn about some

of the phenomena of tumors of endocrine glands I welcome the privilege of conveying to you the result of these observations, not that they have intrinsic worth, but because they provoke thought and may stimulate further investigations in many channels

*Embryology* It is customary in discussion of neoplasia to consider the embryonal origin and development of the structures concerned. However, the newer investigations of embryology have led to abandonment of rigid interpretations of derivation from the three embryonal layers. On the basis of tridermal origins, many of the components of endocrine glands are evidently of epithelial nature. This appears to be true of hypophysis, thyroid, parathyroid, pancreas and adrenal medulla. The thymus is largely a mesoblastic derivative, but the cells of Hassall's corpuscles are epithelial in character regardless of their source. The adrenal cortex is probably a mesoblastic derivative but the morphology of the cells is epithelial and that is true of certain aspects of their behavior. Although the primitive sex-cells are derived from entoderm of the hind gut, yet the development of the mature gonad appears to represent a complex action of these epithelial cells and of mesoblast on each other, so that the final structure contains both components. This leads to certain difficulties in the interpretation of some of the tumors of ovary and testis. Furthermore, the approximation of certain anlagen may be of importance, as illustrated by the tumors in the sella turcica derived from Rathke's pouch. This may be exemplified also in tumors of ovary and testis composed of cells and structures which resemble those of adrenal cortex and the embryonal kidney. The anlagen of kidney and adrenal cortex lie in the genital ridge near that of the sex gland and embryonal displacements or inclusions may possibly occur.

*Genesis of the Tumors* It is generally agreed that two important factors are of significance, an intrinsic factor which evidently prepares the cell for neoplasia and a realization factor which brings it about. Heritable influences have not been clearly demonstrated in connection with tumors of endocrines and there has been no satisfactory explanation of other intrinsic factors. That hormones of one gland may lead to neoplasia in another is now undisputed and insofar as the affected gland is concerned, that is an extrinsic or realization factor. The lack of certain hormones may also be effective, probably because of release of inhibiting influences or because of disturbance of hormonal balance. That other extrinsic factors may operate is indicated by the experimental

irradiation of young mice, with the development in later life of ovarian tumors, which have now been shown to be true neoplasms

Discussion still centers about the exact cells of origin, especially as to whether they are mature, embryonal or dedifferentiated. The tumors may contain cells which appear to be fully mature, as for example in the various forms of pituitary adenomas, the insular adenoma of the pancreas, and the cortical adenoma of the adrenal. These have tinctorial properties and cytoplasmic constituents like those of the adult organ. Conversely, however, morphological anaplasia is not infrequent as in the dysgerminoma of the ovary and the embryonal carcinoma of the testis.

An example of the controversies which may arise is the granulosa-cell tumor of the ovary. There are those who hold that this tumor is derived from mature cells of the granulosa, and this is based on human material and experimental observations. The intricacy of the reasoning is illustrated by the opinion that this tumor is derived from anovular nests of granulosa which persist in the mature organ. Although not yet settled, there is considerable doubt that granulosa will continue to exist without the presence of the ovum. An observation of a tiny granulosa-cell tumor in the hilum of the ovary where granulosa does not naturally occur led to the conclusion that the tumor could not have arisen in mature granulosa. Others believed that the granulosa-cell tumor is derived from nests of mesenchymal cells which subsequently differentiate in the course of neoplastic growth so as to resemble granulosa. Based on the same experimental material in the mouse, one group favored origin from mesenchyme but another believed that the tumors originate in germinal epithelium. Still other investigators, basing their view on experimental material of the same sort, ascribed the origin to undifferentiated parenchyma.

Another better known example is the tumor of the testis, called by some embryonal carcinoma and by others seminoma. Many adhere to the view that this lesion is the result of a one-sided development of a testicular teratoma and there is good evidence in support. There is no conclusive proof that the tumor is derived from seminal epithelium. The fact that many patients secrete chorionic gonadotrophin seems to point toward teratomatous origin.

Still another example is the so-called interstitial cell tumor of the testis. Although experimentally tumors of this sort have been induced,

yet there must still remain some question as to whether the cells of the tumor in man are derived from interstitial cells or from included rests of adrenal cortical cells. It is possible that assays of hormones in patients with these tumors may throw some light on derivation and nature. They have definite androgenic properties and if the androgens can be distinguished as of testicular or adrenal cortical origin in a sufficient number of cases, the situation may be clarified.

Even in those endocrine tumors which are composed of cells like those of the mature organ, no statement can be made as to whether they are derived from embryonal nests, mature cells or dedifferentiated cells.

*Nature of the Tumors* Endocrine glands are subject to neoplastic growth derived from or resembling any of the constituent tissues. Thus there may be benign tumors of epithelial or connective tissue origin, carcinoma, sarcoma and various forms of mixed tumors and teratoid growths. These behave as do comparable tumors in other situations. Even here, there are occasional instances of peculiarities. Thus in the thyroid, adenomas and adenocarcinomas occur which are morphologically like those of other glands. However, the so-called metastasizing struma is peculiar in that the gland may show hyperplasia or adenoma in which no clear features of carcinoma are microscopically evident. Yet blood vessels are invaded and metastasis occurs.

Many of the tumors are derived from tissues which are of epithelial character or derivation. In the benign form these are usually called adenoma, even though they may have no acinic structure whatever. Examples are found in the various forms of adenoma of the pituitary and the cortical adenomas of the adrenal. The malignant forms, however, are called carcinoma without the prefix adeno. Other tumors which are evidently derived from cells of epithelial origin are not called adenoma or carcinoma. Thus the peculiar neoplasms of adrenal medulla are named pheochromocytoma, chromaffinoma, sympathicoma or ganglioneuroma, and the malignant forms by common custom are indicated by the suffix blastoma, as pheochromoblastoma or sympathicoblastoma. Then there are tumors the origin of which is so obscure that they are named according to type of cell. This is exemplified in the granulosa-cell tumor and the theca-cell tumor, or thecoma, of the ovary. There are still others in which the very character of the cells is far from clear. Here must be placed a tumor of the ovary composed of large cells with a lipid-containing vesicular cytoplasm, cells which morphologically re-

semble both cells of the adrenal cortex and of corpus luteum. These are sometimes called hypernephroid tumor, adrenal cortical adenoma, interrenaloma and have also been given the name masculinovoblastoma, a curious mixture of morphological and functional terminology.

*Malignant tumors* As indicated above, many tumors of endocrines have the features common to tumors elsewhere which indicate whether they are malignant or non-malignant. There are others, however, in which this distinction is not altogether clear. The metastasizing struma is a case in point. The pituitary adenoma is usually localized in the gland or if large is confined by the capsule of the organ. Yet there are occasional instances in which capsule is penetrated and surrounding bone invaded. Thus the tumor has at least one important feature of malignant disease, namely invasion. However, it is usually impossible by microscopic examination of the tumor itself to detect a pattern of arrangement, pleomorphism of cells, abnormalities of mitotic figures or other features common to malignant tumors which would lead to a positive diagnosis. In some of the pheochromocytomas of the adrenal, pleomorphism is conspicuous, but the tumor is fully encapsulated, does not metastasize and does not recur after removal. Yet invasive tumors of this order will have microscopic features identical with the non-malignant form. Metastasis of some of the malignant tumors, such as the neuroblastoma of the adrenal or the carcinoma of the thyroid or the choriocarcinoma of the testis may be widespread, but certain other tumors, such as the malignant granulosa-cell tumor of the ovary, may show but little tendency to early or extensive metastasis.

Recurrence after removal poses a special question. Not long ago a pheochromocytoma of the adrenal was removed surgically in one of our clinics, but at operation a smaller tumor of identically the same nature was found near the renal pedicle. No answer can be given to the question as to whether this smaller mass was metastatic or originated in an aberrant medullary mass. The presence of supernumerary or aberrant adrenal tissue is well known and confuses the pathologist when he is confronted with the problem of metastasis, recurrence, or a new tumor in an accessory site.

Reports on granulosa-cell tumor of the ovary indicate recurrence in as much as 38 per cent of the cases. Whether this is actually recurrence or the development of a new tumor is an open question. If this tumor is actually derived from mesoblastic cell rests with the potentiality

of developing into cells with the morphology of granulosa, there is the distinct possibility that what is thought to be a recurrence is a new tumor derived from another cell rest. This is emphasized by the fact that granulosa-cell tumors have been found primarily in broad ligament and hilum of ovary. In order to be sure that there is recurrence, evidence must be adduced to show that the original tumor had malignant features. The difficulties in this direction have been indicated above. When penetration of capsule, direct invasion and metastasis are present, the diagnosis is unquestioned. Yet these may not be evident in a surgical specimen. As the result of a large experience, I have formed the opinion that in many of the peculiar tumors of endocrine glands, the most distinctive feature of malignant disease is invasion of the capsule rather than alterations of cytology. Before accepting a diagnosis of recurrence, I would wish to have clear indications of malignant disease in the original tumor.

Thus it is evident that percentages of benign and malignant forms of several of the tumors of endocrines must be determined by critical analysis of all the facts available.

*Place of Function in Identification* Although some of the tumors of other glands may exhibit function of a sort, as in mammary neoplasms, yet special forms of tumors of endocrines display functional activities which are identical with or closely simulate those of the gland from which the tumor is derived. This necessarily brings the oncologist into the field of endocrinology. However, he recognizes that just as there are unexplored areas of oncology, so there is much yet to be learned about endocrinology. Internal secretions are subject to metabolic changes, and what is recovered in the blood or urine is not necessarily the exact substance produced by the gland. Methods of assay have been vastly improved, but the techniques for the most part are as esoteric as the field itself. Simplification without loss of precision, and even improved accuracy, are essential to more widespread use. Furthermore, the entire series of chemical changes up to the point of excretion must be understood. Complete knowledge of these factors provides the only satisfactory explanation of functioning endocrine tumors.

The content of hormone in a given tumor may give a clue as to its activity, but there remain the questions as to whether the tumor secretes a normal hormone in excess, whether the hormone is in its original form or whether the material extracted represents formative constituents for

production of normal hormones, whether there is a pattern of constituents which may be significant, and whether the tumor serves principally as a storage place. Extractions from tumors often yield such minute amounts of steroids or hormones that distribution of fractions cannot be determined. The use of autopsy material is limited by the fact that by the time of death what appeared originally to be disease of one gland has usually become polyglandular.

Thus the most productive studies are those made during the life of the patient. Yet even so, the tumor must be identified morphologically. There are instances in which morphological diagnosis is difficult or even impossible. What then can be done? It seems like arguing in a circle to say that a tumor devoid of specific morphological characterization belongs in a certain group because it has exhibited the functional effects ascribed to that group. Exact information cannot be collected or analyzed on that basis. It were better to leave such tumors unclassified than to read into them interpretations which are largely hypothetical. Although it must be admitted that certain clinical complexes with definite functional manifestations, as for example some of the disorders of cardiac conduction, cannot be given a clear cut morphological background, yet it is certain that most diseases have an identifying morbid anatomy. This serves both pathological and experimental investigations. The disease induced in animals must closely resemble that of man, if satisfactory deductions are to be drawn. There is no good reason why this does not apply to functional endocrine tumors, and much of what follows is based on that premise.

*Morphology* The functional tumors may be incorporated in a gland without either encapsulation or pressure effects on the rest of the organ. This is particularly true of some of the pituitary adenomas. In such an instance, however, the question often arises as to whether the lesion is a localized hyperplasia or a neoplasm. Usually this question is resolved only by the personal opinion of the observer. However, when the growth replaces the entire pituitary and attains such size as to produce enlargement of the sella turcica, there is no dispute, but even in these instances there may be a surrounding rim of non-neoplastic cells. When the lesion is definitely nodular, morphologists generally agree that it is neoplastic, as for example, the thyroid adenoma, but functional studies may not entirely support this view.

Other tumors may grow in part of a gland and displace other parts

Thus the cortical adenoma of the adrenal may be partly surrounded by other parts of the cortex and the medullary pheochromocytoma similarly partly surrounded. And this is true of these tumors even when they have a diameter of several centimeters.

The shape of the tumors is generally spherical, but as elsewhere, the configuration of the organ or the influence of surrounding structures may modify the form. As a rule the outer surface is smooth, but there are curious exceptions. Tumors of pituitary, of thymus, of parathyroid, of adrenal and of testis usually have a smooth surface. The granulosa-cell tumor of the ovary when small may be smooth but the larger tumor is nodular. Yet the theca-cell tumor of the ovary usually has a smooth surface. Testicular tubular adenoma of the ovary is usually nodular, but sarcomatoid and mixed forms of arrhenoblastoma have a smooth surface.

The capsule of these tumors is usually the capsule of the gland rather than one stimulated by the presence of the tumor. A noteworthy exception is the thyroid adenoma.

Cytology has been commented on in reference to malignant character. The cells may be uniform and resemble those of the mature gland, but departures are frequent. Pleomorphism and active mitosis may occur in tumors which do not behave as malignant neoplasms. Thus, as has been said above, it is often impossible on the basis of cellular form or arrangement to distinguish between benign and malignant forms.

Just as ductless glands are richly vascularized, so are most of the tumors of these organs. There are of course wide variations in this respect, but the adrenal tumors are noteworthy for plentiful blood vessels. Although not uniformly true, the malignant tumors are generally more richly vascularized than the benign forms. The blood vessels are small and for the most part of capillary size. Occasionally there are large vascular spaces lined only by endothelium. Consequently some of the tumors may exhibit hemorrhage and necrosis, and subsequent hematogenous pigmentation. Naked unlined vascular slits may occasionally be observed but have little significance as an indication of malignant character. There is no clear indication that the tumors accompanied by hormonal disturbance are more richly vascularized than are others.

*Chemical components* These have not been studied extensively. Attention, however, has been paid to lipid content of the cells of certain of the tumors, without throwing great light on their origin. Certainly exact chemical analysis is to be preferred above histo-chemical tech-



niques Attempts have been made to distinguish between the lipid content of the granulosa-cell tumor and the thecoma of the ovary but no truly significant differences have been disclosed The study of the lipid content of cortical adrenal tumors and of the so-called interstitial cell tumors of the testis has given no satisfactory information Even if the lipid content of the normal human adrenal were definitely known, there is no assurance that neoplastic cells of that gland would be chemically identical Nevertheless, further studies may ultimately throw some light on the nature and probable origin of some of the functional endocrine tumors No special information has been obtained by examinations for glycogen Thyroid tumors have been found to contain iodine and thyroxine in amounts approximating those of the active gland

*Content of hormones* Certain insular tumors of the pancreas, including adenoma, carcinoma and its metastases, contain a substance which behaves as does insulin and the clinical manifestations are not distinguishable from those of hyperinsulinism That these neoplastic cells produce an insulin exactly identical with that elaborated by the normal islet cells has not yet been established With an adequate amount of tissue it should be possible to isolate the hormone in crystalline form Then a statement could be made as to whether the neoplastic cells produce true insulin

Medullary tumors of the adrenal contain adrenalin and probably produce it, and the pressor substance discovered in the blood of the patients with spasmodic hypertension behaves pharmacologically as does adrenalin

Estrogenic and androgenic substances have not been identified in the cortical adrenal tumors, even though androgenic substance has been demonstrated in the urine of patients with virilizing tumors or with cortical hyperplasia

Granulosa-cell tumors of the ovary have been shown to contain estrogenic substance in amounts equal to or greater than is true of the ovary, but this has not been proved to be alpha estradiol

The content of thyroxine in thyroid tumors has been mentioned without maintaining that this is the one effective hormone of the thyroid

None of these observations has yet established positively whether the tumor elaborates the hormone or is simply a place of storage, but the former seems likely In certain measure, however, the same may be

said of the non-tumorous gland

*Immunological Properties of Cells* Chromophobe adenomas of the pituitary produce signs and symptoms because of their mass. The same may be true of acidophilic and basophilic adenomas. In addition, however, the acidophilic adenomas are commonly associated with acromegaly. Thus it is assumed that the acidophilic cells produce the growth promoting hormone of the gland. There are rare instances of acromegaly in which the adenoma is not acidophilic. This is explained by the statement that the cells have become so exhausted that they no longer take the acid stain, which may well be true. There is no conclusive proof of the explanation and doubt is thrown on the complete validity of the original assumption. Of course, improper fixation and faults in staining technique may be responsible, but that statement also begs the issue. It is conceivable, however, that cells originally acidophilic may, when they undergo neoplastic proliferation, lose their immunological peculiarity without alteration of their functional capacity. Furthermore, if as has been suggested, the chromophobe cell is the precursor of the acidophilic and basophilic cells, an adenoma, not acidophilic, may perhaps be looked upon as made up of immature cells without fulfillment of potential morphological differentiation but with the functional capacity of the mature cell.

Basophilic adenomas of the pituitary are commonly associated with Cushing's disease, but there are instances of the disease in which no such adenoma is found. Much more uniform is the coincidence of cortical hyperplasia of the adrenals. In one of our cases, the cortical hyperplasia was extreme and only by serial section was a tiny clump of basophilic cells discovered in the pituitary. This was so small that reasonable question was raised as to whether it was a focal hyperplasia or a neoplasm. A recent study points toward the view that Cushing's disease is the result of functional disturbance of the hypothalamic region and that the basophilic adenoma when present, even with the hyalinization of cytoplasm of basophilic cells, the so-called Crooke change, is secondary, as is probably true of the cortical adrenal hyperplasia.

There is ample evidence of the fact that the production of insulin is governed by the beta cells, yet the insular tumors of the pancreas may contain but few cells with characteristic beta granules. The question then arises as to whether the cells which constitute most of the tumor are derivatives of original beta cells, morphologically altered in

the course of neoplastic proliferation, whether they originate in other insular cells which have assumed new function, or whether they are a new race

It has been claimed that cortical tumors of the adrenal, accompanied by virilization, contain cells peculiar in their affinity for fuchsin, the so-called fuchsinophile cells, and there is no doubt that such cells exist. The interpretation that they deal with virilization, however, is not sufficiently well founded. The staining technique can be manipulated so as to show these cells in the common non-functional adenomas of the adrenal cortex and indeed in medullary tumors, as well as in other organs of the body. At least, the association of fuchsinophile cells and virilization is not proved.

*Physiological Manifestations* The effects of the functional tumors of the endocrines are necessarily related to their production of hormones, natural or altered, but it is not necessary to assume that these act directly upon other endocrines or upon other tissues or organs. It may be that in many instances the effects depend upon alterations of the internal environment of the body. In this sense, certain glands may act as synergists or antagonists. Ovary and adrenal cortex are said to be synergists. If this be so, hyperfunction of the ovary, as mimicked by prolonged injections of estrogens, may lead to brown degeneration of the adrenal cortex, probably a manifestation of hypofunction of adrenal cortex, whereas inhibition of ovarian secretion by ablation is often followed by nodular hyperplasia of the adrenal cortex, probably as an index of hyperfunction. The former effect may well be due to direct effect of estrogens, whilst the latter is probably the result of an alteration of internal environment. It must be said, however, that this example is not accepted by all endocrinologists and that the principal examples of synergism are to be found in certain internal secretions of the pituitary, e.g., the two gonadotrophins. An example of antagonists is to be found in pancreatic islets and adrenal medulla. Active function of the latter raises blood sugar, but insulin lowers it. Lowering of the blood sugar by insulin stimulates the adrenal medulla, but this stimulus is due to the blood sugar level, an alteration of internal environment, rather than directly to insulin.

There must also be involved a state or condition of receptors for hormones or receptors for the stimulus of altered internal environment. This appears to be illustrated in the statement that acidophilic adenoma

of the pituitary is accompanied by gigantism if it occurs in early life and by acromegaly if in later life. The importance of the state of receptors is probably a general principle of endocrinology as witnessed also in such manifestations as unilateral exophthalmos in Graves' disease and in the occurrence of unilateral gynecomastia.

As said above, the products found in blood and urine are not necessarily the exact hormones produced by the glands. All these facts must be recalled in any interpretation of clinical phenomena.

*Virilization* This is broadly interpreted to mean sexual precocity in males and the appearance of certain masculine characters in females. In connection with the latter it must be recognized that some women are hairy, broad shouldered and have deep voices, evidently on the basis of constitution and heredity. It is a mistake to assume that they harbor virilizing tumors, although it must be admitted that the features may be due to endocrine disturbance.

Precocity in boys may accompany cortical adrenal tumors and the so-called interstitial-cell tumors of the testis. The boys are above average stature and have an advanced bone-age and mental age. The face is mature in appearance and the voice deep. Sometimes the boys have a slight beard. Hair grows in axilla and on the chest, and a male escutcheon appears. The external genitalia are large and erections are more frequent than would be expected for the age. Although it has been said that ejaculations containing spermatozoa have been observed, this seems unlikely, because if there is an excess of male sex hormone spermatogenesis should be depressed.

Virilization of females occurs in children, in young women, and in some measure in older women. It is an accompaniment of cortical adrenal tumors and of tumors of the ovary especially the arrhenoblastoma and the so-called hypernephroid tumors. The clinical features in children include those of the so-called adreno-genital syndrome, such as broad shoulders, narrow hips, growth of hair in axilla and on pubis, prominent mons veneris and large clitoris. Musculature is well developed and in these cases, as in the precocious boys, the figure is indicated by the term "infant Hercules." The voice is sometimes deep.

In young women, after the menarche, the physical signs described above as occurring in children are much the same but may be noted as a distinct change from previous feminine characters. Included also is amenorrhea. Natural libido may be preserved, may be absent, or is said

in some cases to be inverted. In women past the menopause, the principal manifestation is hirsutism, which may be accompanied by deep voice and enlarged clitoris.

In children, the tumor is usually the cortical adrenal tumor. In young women it may be either that tumor or one of the ovarian neoplasms. In older women, it is frequently the hypernephroid tumor of the ovary.

*Feminization* This term is only relative and subject to wide interpretation. It may be taken to include precocity in girls, acquisition of female characters in sexually immature adult females, so-called rejuvenation in women in post-menstrual life, and the production of certain somatic changes in males.

Sexual precocity in female children is well illustrated by the effects of the granulosa-cell tumor of the ovary. The child may show increased stature, but the more striking change is in the bodily configuration with broad hips, long fingernails, enlarged breasts, growth of hair on pubis, large mons veneris and large clitoris. Associated is periodic uterine bleeding, usually scanty, lasting a day or two and recurring every three or four weeks. In order to interpret these features as those of premature sexual development in the true sense it would be necessary to have ovulation with the flow. Ovulation has not been proven and is unlikely if there is an excess of estrogenic substance in the blood. By investigation of human subjects and experimental animals there is little doubt that there is an alteration of internal environment due to production of estrogenic substance by the tumor.

However, similar changes may be observed with cortical adrenal tumors, with pituitary tumors, with alteration of pituitary function and with lesions of the hypothalamic region. Also, it must be recalled that in most cases of precocity no tumor or other organic basis is found.

Women of post-menopausal years are said to be rejuvenated, but this term is literally incorrect. The principal phenomenon is irregularly periodic or continuous uterine bleeding. The atrophic ovary cannot produce ova and the bleeding is necessarily anovulatory. The patients do not regularly show psychic or other manifestations of a return of sexual life. The associated tumor is usually the granulosa-cell tumor of the ovary.

Rarely women attain adult life with none of the primary or secondary sex characters. This may be due to hypophyseal dysfunction or absence or failure of development of ovaries. In one instance, a woman

30 years old developed a choriocarcinoma in the pelvis, exact origin not determined, and then had enlargement of breasts, growth of pubic and axillary hair, and irregularly periodic but slight uterine bleeding. Postmortem examination of the pelvic organs disclosed no ovaries and the bleeding must have been anovulatory. There was an increased output of chorionic gonadotrophin and of estrogen with suggestive increase in pregnanediol, but no increase in 17-ketosteroids. Thus the somatic changes are explained. Other comparable cases have been reported but without the assay of hormones.

So-called feminization in males is rather a reduction in maleness than a sexual inversion. The principal changes are atrophy of testes, reduction or absence of libido and gynecomastia. These have been described in two cases of cortical adrenal tumor and are frequent in cases of choriocarcinoma, either in testis or in extragenital position. In a few cases, assays have shown increases in chorionic gonadotrophin and of estrogens. Of interest is the fact that the gynecomastia is usually bilateral, in contrast to the frequency of unilateral gynecomastia in cases without obvious endocrine changes.

*Blood pressure* Changes in blood pressure are usually accompanied by other phenomena. Thus, with the spasmodic hypertension observed with tumors of the adrenal medulla, usually not malignant, there are often headache, dyspnea, nausea and vomiting, vasomotor phenomena, glycosuria and collapse. These correspond to the phenomena produced by overdosage of adrenalin. Thus it may well be assumed that at intervals there is an increased output of adrenalin by the tumor. Occasional instances of continuous hypertension have been reported. This might well be due to liberation of adrenalin, in the sense of a continuous infusion. Although repetition of effective doses in experimental animals is followed by reduced elevation of blood pressure, this phenomenon is not observed if the doses are minute as would be true in infusions over a long period. In some of these cases the persistent hypertension may be incidental.

Persistent hypertension occurs in patients with Cushing's disease but as indicated above, the basophilic adenoma of the pituitary has not been conclusively shown to be the primary event. In some instances, acute and chronic arteriolar disease has been found in the kidneys, but this is by no means regular and cannot explain all cases. It occurs frequently with adrenal cortical tumors probably due to excessive production of

steroids Although experimentally desoxycorticosterone acetate will produce elevation of blood pressure, it has yet to be shown whether desoxycorticosterone or some other steroid operates in the tumor cases

*Metabolism* Increased basal metabolic rate accompanies certain adenomas and some of the carcinomas of the thyroid and is evidently due to production in excess of thyroid hormone There is some dispute, however, as to whether this increased production is solely by the tumor or by the gland as a whole

Certainly the metabolism of sugar is altered by the activity of certain adenomas and carcinomas of the pancreatic islets Depression of insular function may occur with other tumors Diabetes is a frequent accompaniment of tumors of the pituitary, of Cushing's disease and of tumors of adrenal cortex The temporary glycosuria which may be associated with paroxysms due to pheochromocytoma is not a true diabetes

*Fat metabolism* may be altered in both directions The loss of fat in hyperthyroidism appears to be due to increased metabolic rate rather than to direct effects of the hormone Obesity occurs in connection with adrenal cortical tumors and some of the ovarian tumors Dystrophia adiposogenitalis (Frohlich's syndrome) may sometimes be associated with tumors, but this is not always true What part hormones play is somewhat uncertain, but the removal of virilizing tumors in young women is followed by deposit of fat in breasts and about hips It has been shown that the fat deposits can be utilized in metabolism as in other fat Although patients with Cushing's disease may appear to be obese, as exemplified in the "moon face," there is a mass of opinion to the effect that edema plays a larger part than accumulation of fat As with other people, patients with endocrine tumors may become obese because of overeating and lack of exercise

*Protein metabolism* In hyperthyroid states, such as may accompany thyroid tumors, there is an increased destruction of proteins as indicated by augmented excretion of nitrogenous products in the urine In certain diseases in which diabetes is part of the picture, protein may be utilized in the production of glucose This gluconeogenesis may be responsible for loss of cutaneous resiliency and the occurrence of abdominal striae and cutis marmorata in Cushing's disease Perhaps muscular weakness may have the same cause It has been called upon to explain osteoporosis and certain other phenomena

*Electrolytes* In occasional cases of Cushing's disease, chloride and potassium are affected, but there is no regularity as to increase or decrease. The importance of tumors of the parathyroids to calcium and phosphorus metabolism is well known. Experimental evidence indicates that these changes are due to the hormone of the parathyroids and that the changes in bones and the formation of renal calculi are the result of the concomitant alterations of internal environment.

*Growth* As has been mentioned, growth is promoted by pituitary tumors, especially the acidophilic adenoma, by some of the cortical adrenal tumors of early life and perhaps by ovarian tumors in childhood. Experimental investigations of the effects of various hormones sometimes yield contradictory results and show variations in different species. Thus there is difficulty in applying these studies to man. There is probably a considerable interplay on the part of different glands and a synergism of different hormones of the same gland, as for example, the pituitary. Thus it is said that the growth hormone of the pituitary is favorably influenced by other secretions of the pituitary. In addition there are probably also genetic factors of significance.

*Concluding Comment* Endocrine glands may be the seat of primary and metastatic tumors such as occur in other structures, but in addition there is a relatively small number of neoplasms of these glands which display striking functional activity. In the sense that hormones are soluble products of specialized tissue, which through the circulation affect other tissues, the tumors undoubtedly produce hormones, but in many instances there is no proof that these are identical with hormones produced by the normal gland. The clinical and metabolic effects are generally like those of natural hormones. However, there are variations even with the same type of tumor, which suggest either departure from the natural chemical composition, alterations in metabolism of the hormone itself or changes in receptor mechanisms, or combinations of these factors. Nevertheless, the clinical picture and various methods of examination of the patient may lead to successful surgical or other forms of treatment. Most of the tumors can be identified morphologically. The endocrinologist may ultimately provide the clew to the positive diagnosis of those neoplasms of endocrine glands which still puzzle the morphologist and clinician. As is true of other fields of medicine, intelligent cooperation is the key to further progress.



RECENT ADVANCES IN THE USE OF  
CURARE IN CLINICAL PRACTICE\*

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ON the basis of his experiments, Claude Bernard<sup>1</sup> concluded that curare acts upon neither nerve nor muscle but upon an entity we call today the myoneural junction. This concept is still acceptable. He then outlined future investigation in stating that it was first necessary to isolate the active chemical principle of the crude drug, after which the crucial experiment would be to determine the nature of its action, physical or chemical, on the myoneural junction.<sup>2</sup> The first important step was taken by King,<sup>3</sup> and Wintersteiner and Dutcher,<sup>4</sup> in isolating and identifying the pure crystalline tubocurarine. Previous to this, knowledge of the alkaloid was confused both as to exact botanical origin and pharmacologic properties. Now for the first time it was possible to evaluate a curare of known purity and predictable effect. The final step, or determination of its mode of action on the myoneural junction, is still incompletely realized.

Tubocurarine belongs to a group of compounds known as quaternary ammonium salts. In general, these salts exhibit the property of paralyzing neuromuscular conduction at the myoneural junction.<sup>5</sup> The majority, however, have other properties which overshadow and obscure this action. Almost alone among them, tubocurarine, in certain concentrations, has a pure myoneural junction effect.

What do we know of this property? It is most probably related to the configuration of the molecule rather than merely to chemical composition. Acetyl choline and prostigmin have similar configuration and under certain circumstances can be made to exert a curariform effect, and conversely, curare can be made to cause a muscle twitch.<sup>6</sup> The physical chemists have shown that molecules of this stereochemic type exert specific effects on vital membrane structure. Further study of these membrane phenomena will undoubtedly add to our knowledge of how

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the quaternary ammonium salts act. The implications of these facts are of physiological import because any data about the nature of neuromuscular conduction throws light on the entire problem of synaptic transmission in the central nervous system.

### THE NATURE OF CURARE BLOCK

Let us briefly outline one line of reasoning based on experimental facts. The myoneural junction is an excitable membrane. A transmitter substance, whether it be acetyl choline or local action currents, induces a potential by actively depolarizing the junctional region. Normally, this depolarization reaches a critical value and produces the muscle spike by spreading electronically and depolarizing the neighboring area. In fully curarised muscle, this so-called endplate potential rises to a sub-threshold level and then decays without initiating a muscle response. If curare merely paralyzed skeletal muscle in this manner, it would have little clinical value in the type of cases to be discussed here. However, the size of the endplate potential depends, to some extent, on the concentration of drug.<sup>7, 8, 9, 10, 11</sup> Therefore, the degree of block can be controlled. Frequencies above a critical range, or abnormally sustained, can be blocked, while those of different characteristics will still evoke a normal muscle twitch. Since the normal excitatory state at the junctional membrane depends on rapid reversibility of polarization, any mechanism which either reduces this capacity or maintains the membrane in a single phase for abnormal periods of time acts as a depressant. Such a process may explain why in certain concentrations acetyl choline and prostigmin are depressants of neuromuscular conduction.

These observations underlie the present day concept of curare therapy. We do not attempt to paralyze the myoneural junction, but merely to create a block to the abnormal impulses imposed upon the myoneural junction by the disease process. It is thus perfectly feasible to obtain a therapeutic effect without loss of voluntary power.

### THERAPEUTIC APPLICATIONS OF CURARE ACTION

#### *What is the clinical value of these facts?*

Review of the literature reveals that since the mid-nineteenth century curare has had sporadic clinical trials.<sup>12-17, 14</sup> Because of its narrow therapeutic margin and evanescent effect its usefulness, except in very skilled hands, has been sharply limited in spite of a sound physiological

basis<sup>15, 16, 17, 18</sup>

With aqueous solutions an effective clinical response is usually associated with unpleasant side effects<sup>15, 16, 17, 18</sup>. Absorption is followed by high concentration and rapid elimination. At such high concentration, central and peripheral effects occur concomitantly. Prolonged duration of effect at optimal levels of concentration is thus impossible. In an attempt to avoid the toxic responses and prolong the desired effect, various vehicles were tried in this study. A suspension of d-tubocurarine chloride in white wax and oil proved best.<sup>19</sup> Percentage composition was based on clinical assay in an attempt to achieve adequate peripheral action without superimposed central phenomena or paralysis. The proportions in use today are 3 per cent tubocurarine in 4.8 per cent wax in peanut oil. One cubic centimeter of the suspension contains the equivalent of 175 units of standard curare.<sup>20</sup> The alkaloid is stable and not affected by sterilization. It is well standardized and its action predictable, milligram for milligram. The suspension is given either by the subcutaneous or intramuscular route.

The present series consists, at the time of writing, of 1500 injections ranging from 0.4 to 2.5 cc. of suspension in a group of 200 patients. Dosage requirement seems only vaguely related to body weight, but directly to disease entity. Duration of effect has been from 24 to 168 hours, and likewise related to the type of pathology. It is obvious that the effect seems prolonged over the period that curare is present in the body in perceptible concentrations. This curious fact is being investigated in the laboratory but unfortunately work is slow because no adequate method of blood level determination has been discovered.

The following types of pathology are represented in this series

I Muscle Spasm, as in (a) direct trauma to muscle, (b) low back syndrome, (c) orthopedic deformities with reflex spasm, (d) myositis, (e) arthritis

II Spasticity, as in (a) degenerative diseases of the central nervous system (1) multiple sclerosis, (2) disseminated sclerosis, (3) familial lateral sclerosis, (b) spinal cord injury, (c) cerebrovascular disease, (d) tumors of the brain and spinal cord

III Spasticity with dystonic features (Little's disease, cerebral diplegia)

IV Dystonia and Athetosis

V Rigidity, as in (a) Parkinson's syndrome

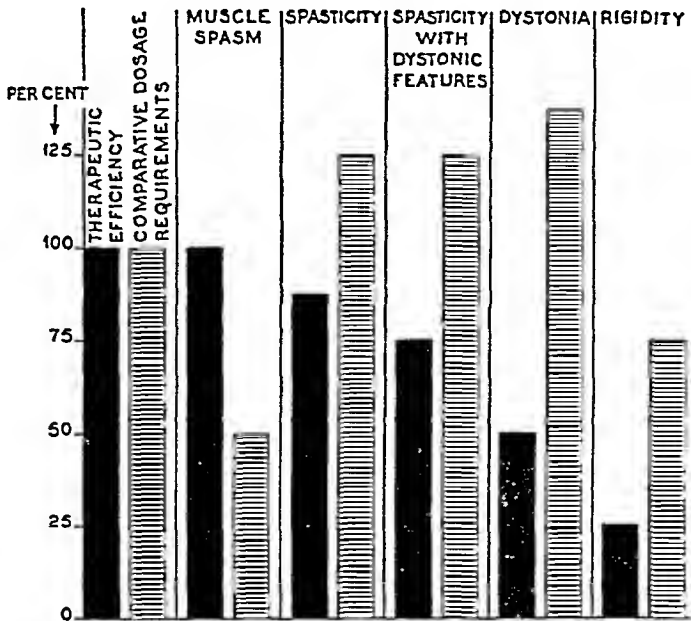


Figure 1 is an attempt to correlate statistically the comparative therapeutic efficiency and dosage requirements in the various types of pathology represented in the series. It is apparent that spasm and spasticity respond much more readily than the more complicated neuromuscular mechanisms. Dosage requirement roughly follows an inverse pattern except in rigidity. Dosage levels in rigidity differ in being a function of therapeutic response within the limits of strikingly early toxic signs and symptoms.

## THERAPEUTIC RESULTS

**I Muscle Spasm** Since curare is a physiological muscle relaxant, it is not surprising that spasm responds so well. The vicious cycle of pain and muscle spasm is well known, as is the rapid relief afforded by any means which serves to break up this cycle. In this series, we have seen all degrees of spasm yield to treatment, although where the pain was based on root compression, residual root pain remained after complete reduction of reflex muscle spasm. This response is useful diagnostically in ruling out root compression as a causative factor in a clinical picture. If, after treatment, pain of radicular type persists in spite of marked diminution of spasm and diffuse pain, it is probable that root compression is the underlying cause. On the other hand, in orthopedic disturbances with reactive spasm, all the pain except focal pain or tenderness at the site of disease seems to disappear.

So many common disorders, based on the wear and tear of our mode

of life, are accompanied by muscle spasm and pain that the usefulness of a drug of specific value in such conditions needs no elaboration

A case demonstrating the value of curare in oil in muscle spasm accompanying low back syndrome is cited

A 48 year old male, member of a medical college faculty, over a period of years has had occasional lumbosacral pain with moderate muscle spasm. These attacks were self limited and disappeared without residue. In recent years patient has grown much heavier and has led a more sedentary existence. In February, 1946, he began to note recurrence of lumbosacral pain. This became increasingly severe over a period of days and patient was admitted to the hospital. On mild sedation, bed boards and rather haphazard traction, he improved enough in three days to be discharged. X-ray examination had revealed an unstable lumbosacral joint with proliferative arthritis in the joint region. Two days later pain had increased to its former severity and patient was again hospitalized. Muscle spasm at this time was more pronounced, and patient was in constant severe discomfort, in all positions. Traction was reinstituted without relief. Morphia and sedation were used in large doses. The orthopedic attendant advised a body spica, full length, and this was applied. The patient complained more and more bitterly, remained sleepless, and unrelieved by any form of medication. At the end of four days spinal anesthesia was contemplated in a heroic attempt to reduce the marked muscle spasm of the entire low back region with the accompanying severe pain. A trial of curare in oil was agreed upon instead. One cc of the suspension was given in the right buttock. Two hours later the patient stated that his back muscles had relaxed and at the same time, the accompanying generalized pain had vanished. The reduction was immediately demonstrable on examination. Patient now noted only focal pain on motion at the lumbosacral articulation. Relief of pain was followed by adequate rest without medication. The patient became less tense, began to eat, and regain his normal equilibrium. However, by the third day, in dread of a recurrence, he requested a second injection. The same dose of drug was given at this time and again three days later. The spasm never recurred and the patient's subsequent convalescence was completely uneventful. A back brace was prescribed by the orthopedist and when this was fitted the patient was allowed up and discharged from the hospital.

II. *Spasticity* With true spasticity it is generally possible to increase

motor efficiency by eliminating the increased excitability of the stretch reflex. Whatever the patient's motor power, it is always possible to increase its utilization by reducing the spastic element. Voluntary power is unaffected at dosage levels, sufficient to relieve spasticity. In every case in the series, gait was improved by this unmasking effect. Retraining enhanced this new level of performance strikingly. It was of interest to hear the patients repeatedly describe the degree of muscular relaxation present after the first injection. Characteristically, those with spastic lower limbs called attention to their ability to wiggle their toes or perform heel to shin tests previously impossible. This suppleness, once regained, survived in spite of termination of treatment, even though there may have been a return of considerable degree of general spasticity.

A case illustrating the effect in spasticity secondary to degenerative disease of the central nervous system is illustrated. A 38 year old male was admitted to the Neurological Institute with chief complaint of difficulty in walking. For the last 14 years he had noted increasing spasticity of the lower extremities, along with weakness, especially on the left side. One brother and a sister had the same complaints. On examination, patient walked with a marked scissors gait, with his feet crossing on forward motion. There was pronounced adductor spasm. The left leg did not flex and elevate on forward motion but instead dragged forward. There was a paucity of associated movement of the extremities. Only the toe region touched the floor during ambulation, and the heels were held three inches above the floor even with effort to walk on the entire foot. The trunk was thrown forward and there was an increase in lumbar lordosis. Clonus and increased reflexes were noted. A diagnosis of familial lateral sclerosis was made. Patient was started on 1 cc of curare in oil twice weekly and continued on it for four weeks. Re-education exercises in walking were given daily. Adductor spasm was rapidly reduced. Electromyograms demonstrated a drop in hyperexcitability of the stretch reflex in the lower extremities. The patient noted increased flexibility and could perform knee chest exercises and wiggle his toes freely for the first time in years. The gait rapidly changed with reduced scissors tendency and with both heels fully touching the ground in walking. In four weeks the dose was dropped to 0.6 weekly which seemed to maintain the patient at an efficient level of response. The patient was discharged in six weeks on weekly doses of 0.6 cc administered on an out-patient basis. At the time of discharge, analysis of

moving pictures of the patient's gait revealed striking improvement. The exaggerated lordosis was gone and at rest the patient stood with legs apart and toes pointed outward. Passive stretching of the adductors did not initiate abnormal responses. In walking associated movements had returned, and both feet were firmly on the ground without the previous marked inversion tendency.

In *spastic paraplegia*, the use of curare in oil has proved a valuable adjunct to treatment. These cases have always been most difficult to handle, and no adequate measure has yet been described which will alleviate the distressing reflex manifestations of this condition with complete success.

In these cases it has been possible to (1) reduce mass movements and thus aid healing of decubiti and prevent sudden expulsion of urine, (2) prevent contractures, and (3) permit active physiotherapy without acceleration of reflex spasm.

In *spastic paraparesis*, the results are even more successful. Since there is residual motor power, surgical measures designed to relieve spasticity take a toll in reducing voluntary power. It is here that curare therapy proves most valuable, by relieving crippling spasticity without sacrificing motor power.

A series of cases with an analysis of results has previously been reported.<sup>20</sup> The following case illustrates the usefulness of the drug in these cases.

A 34 year old male had suffered for 12 months from a traumatic lesion of the spinal cord at T-2 due to a gun-shot wound. A laminectomy within 48 hours after injury revealed edematous, discolored spinal cord in continuity. Within three months, there was return of crude sensation and voluntary power was noted in the left foot. Voluntary power increased regularly and within nine months patient could move all muscle groups. However, the return of motor control was accompanied by increasing spasticity in flexion. Ulceration of the mesial aspects of both knees, secondary to adductor spasm, supervened. Fibrosis and contracture at the knee joint followed the prolonged spasm. The patient complained bitterly of pain and attempted suicide in depression over the progress of events. Curare in oil was started and a dose of 1.25 cc arrived at estimation of clinical effect. The patient began to note relaxation of spasm at 45 minutes and maintained it for an average of 72 hours. His subjective symptoms disappeared at the same

time He was encouraged to move about freely and to exercise actively He noted no increase in paresis during his periods of relief from spasticity Physiotherapy was started and vigorously pursued during these periods The ulcerations of the knee region healed spontaneously as adductor spasm was dissipated Muscle tone and volume improved Over a period of 2 months, there was a perceptible decrease in spasticity over and above drug effect In spasticity, duration of beneficial effect is usually of long duration and in general, patients do not return to their original level of dysfunction when therapy is discontinued

### III *Birth injuries, cerebral diplegia or spasticity with dystonic features*

In his monograph on disorders of the central nervous system in children,<sup>21</sup> Crothers states " it is essential to develop every motor asset in sight This conservation and development of assets is procured by two different but closely coordinated methods first and always, by training, and second, by procedures which avoid or correct contractures" Achievement of both these objectives is facilitated by the use of curare in oil Training capacity is markedly enhanced by the reduction of abnormal activity, with a consequent increase in motor efficiency The same reduction in spasticity or abnormal muscle tensions also allows a range of motion and activity which prevents further fixation deformity or contracture Unlike surgical procedures designed to this end, it is unnecessary to destroy innervation or reduce the number of functioning motor elements contributing to the deformity Effective diminution in abnormal motor activity can be obtained without perceptible loss of motor power

One has only to watch these children at school to realize the titanic effort which goes into every attempt at motor performance In light of this, the degree of their achievement under this form of therapy might seem slight to the casual observer Nevertheless, by objective performance standards the improvement in motor performance is striking The same tremendous drive which characterizes their usual effort now pushes their performance levels forward at rapid rates

Improvement can be expected in the following sequence (1) speech, (2) ability to sit quietly, (3) gait, and (4) eating, writing, and performance of all skilled motor activities These patients have maintained their improvement on doses twice weekly

### IV *Dystonia and Athetosis* It has been possible here to (1) Re-



## SUMMARY OF THE PRESENT STATUS OF OUR KNOWLEDGE OF THE FACTORS CONTROLLING BLOOD PRESSURE \*

GEORGE A. WOLF, JR

THE sequence of events which presumably occur when the blood pressure rises is illustrated in Figure 1. In brief a stimulus may activate receptors, impulses from which arrive in the integrative areas of the central nervous system and presumably are distributed via humoral and nervous means to the peripheral vessels. There vasoconstriction and increased peripheral resistance result in elevation of the blood pressure. Other factors which are known to increase blood pressure are included in the diagram.

It is proposed to discuss the events in this "reaction chain" in terms of the role they play in increasing the blood pressure. Environmental stimuli which are known to cause brief elevations of the blood pressure are cold, inhalation of irritant gases, pain, muscular activity<sup>1</sup> and stress producing life situations associated with emotions. Most recently attention has been focussed upon the latter group of stimuli. It has been observed that situations which give rise to anger, aggression, rage, resentment, and frustration are frequently associated with elevations of the blood pressure and an over response of the blood pressure to exercise.<sup>2</sup> These reactions may be sustained. Furthermore, many patients with hypertension have been found to have personalities distinctive in that they are easily aroused to anger and resentment. Such patients restrain their feelings but are subject to temper outbursts.<sup>3,4</sup> Increased cardiac output and increased peripheral resistance play a role in the genesis of this type of hypertension.<sup>2</sup>

There is no evidence that receptor organs are concerned with the regulation of blood pressure other than the fact that they receive stimuli from the external environment.

Integrative function refers to that function of the central nervous

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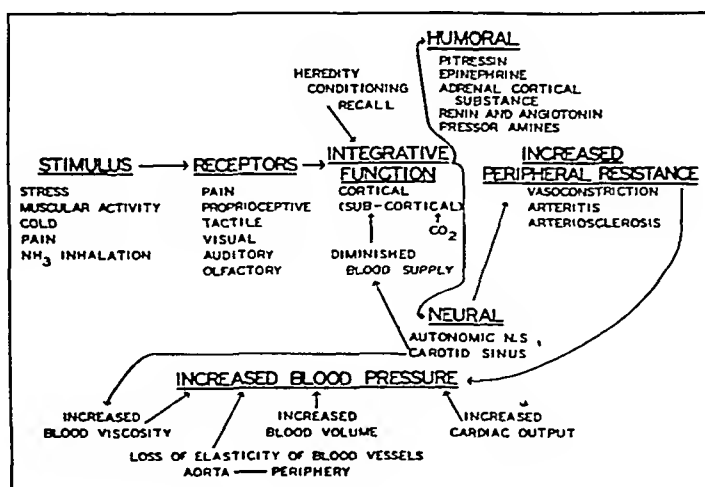


FIGURE I

system which concerns itself with the modification of impulses resulting from environmental stimuli. Interpreted more broadly it may refer to that mechanism which governs the quality and quantity of the reaction of an organism to a given stimulus. Relevant to the problem of blood pressure control it can only be said that conditioning and heredity may exert their influence on this function. Some data are available, however, on the subcortical mechanisms which control blood pressure. Reduction in the blood flow<sup>5</sup> to the vasomotor "centers" and increase in the carbon dioxide content<sup>6</sup> of the blood supplying these areas may give a pressor response. Anatomic evidence of impaired blood supply to vasomotor centers cannot be found in patients with hypertension.<sup>7</sup> It is probable that these areas can be activated by impulses arising in the cortex and influenced by pressor substances in the blood. In addition it is possible that impulses mediated through this area may activate humoral as well as neural mechanisms.

Renin produced by altering the renal blood flow when incubated with hypertensinogen produces hypertensin (angiotonin) which is a pressor substance. Small amounts of renin have been detected in the renal vein after temporary arrest of the renal blood flow in humans.<sup>8</sup> However, attempts to detect renin and hypertensin in the blood of patients with essential hypertension have met with failure.<sup>9</sup> In the blood of patients with glomerulonephritis and malignant hypertension renin,

angiotonin and protein vasoconstrictor substance have been detected<sup>9,10</sup> There is no definite evidence that anatomical impairment of the blood supply of the kidney is present in essential hypertension, and indeed study of the renal blood flow by indirect methods does not reveal functional impairment of the renal blood flow in essential hypertension in the initial phases of the disease<sup>10</sup> It is not clear, however, that an absolute reduction in the renal blood flow is necessary to the production of renin in animals as it can be produced by lowering the pulse pressure in the renal arteries<sup>7</sup> Hypertensin acts directly upon the blood vessels causing vasoconstriction,<sup>11</sup> and its pressor activity may manifest itself in animals with neurogenic hypertension effected by section of the moderator nerves<sup>12</sup> It is further possible that neural processes may initiate vascular changes leading to the production of renin

Pressor amines have been found in the ischemic kidney<sup>13</sup> and the *in vivo* study of these substances has revealed that deaminization occurring in the presence of oxygen has resulted in a loss of the pressor properties Although substances such as these may be active in the control of blood pressure their pressor effect includes an increase in cardiac output and a diminution in the peripheral blood flow not found in essential hypertension<sup>14</sup> That these substances are relevant to the control of human blood pressure has not been shown

Pitressin and epinephrine produce vasoconstriction directly This occurs in the peripheral vessels reducing the peripheral blood flow and in addition may affect the renal blood flow Evidence that hypersecretion of the pituitary and adrenal medulla occurs in essential hypertension has never been found and the vascular changes produced do not resemble those found in essential hypertension<sup>10</sup> On the other hand, patients with hypertension who developed Addison's disease have been shown to have a recurrence of their hypertension when substitution therapy with desoxycorticosterone was provided<sup>15</sup> Adrenal ischemia will produce hypertension in dogs<sup>16</sup>

The recent detection of a substance (VDM) in shock in animals has led to the postulation of a normal balance between vasoconstrictor substances and vasodilator substances It is suggested that alteration in this balance by overproduction of vasoconstrictor substances or diminished formation of vasodilator substances may result in the hypertensive state The vasodilator substances were found in greatest concentration in the liver of the shocked animals<sup>17</sup>

Impulses mediated through the sympathetic nervous system result in vasoconstriction. This may occur in the splanchnic bed, peripheral arterioles and in the renal arterioles. Thoraco-lumbar sympathectomy does not increase the renal blood flow but it may result in a fall of blood pressure.<sup>11</sup> Section of the moderator nerve to the carotid sinus results in a persistent hypertension (4 years in animals),<sup>18</sup> and in one instance bilateral section of the glossopharyngeal nerves in man resulted in a sustained hypertension (4 weeks).<sup>19</sup> The problem exists as to what part the splanchnic circulation as contrasted to the peripheral circulation plays in hypertension.

There seems to be little doubt that elevation of the blood pressure in hypertension is caused by increase in the total peripheral resistance of the arteriolar bed, which in the early stages is functional and not anatomical in nature. It has been suggested that changes in the distensibility of the great arteries alter the cardiodynamics.<sup>11</sup> It is probable that the sensitivity of the arterioles in hypertension is not increased to ordinary pressor stimuli. An arteriolitis can cause an elevation in blood pressure but it is probable that such changes do not occur early in hypertensive disease.

Other changes which serve to increase the blood pressure but which do not seem to be relevant to the problem of essential hypertension include increased blood viscosity, increased blood volume, loss of elasticity of the vessels, and increased cardiac output.

In considering the problem of hypertension in relation to those mechanisms which control blood pressure, one is impressed with the idea that early essential hypertension is a functional state. Indeed the notion of balance or interaction between the various mechanisms of blood pressure control and the notion of reaction of the total organism to his environment are attractive. Such statements are speculation and that unknown mechanisms of blood pressure control are present is quite possible. However, it is becoming increasingly doubtful that a single defect in those factors controlling blood pressure is the cause of hypertension.

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## APICAL SYSTOLIC MURMURS IN INCIPIENT RHEUMATIC HEART DISEASE \*

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**A**N apical systolic murmur, as the initial and sole sign of early rheumatic heart disease, deserves wider recognition than it has usually been accorded. This discussion will be confined to the diagnostic significance of apical systolic murmurs in cases of incipient or dormant rheumatic heart disease, in which the signs of advanced valvular disease—heart failure, enlargement of the heart, diastolic murmurs, and abnormal electrocardiograms—are not present to confirm the diagnosis.

Wartime conditions afforded an unprecedented opportunity to observe cases of incipient heart disease which under ordinary circumstances would not come to a physician's attention. Lessons learned from experience in the armed forces are equally applicable in civilian life where persons with incipient or dormant heart disease will likewise develop disability when overtaxed by heavy physical work or undue mental or emotional stress.

The significance of the loudness or intensity of the systolic murmur is to be evaluated, not its transmission, since the latter depends solely on the loudness of the murmur.<sup>1</sup>

The importance of the problem is emphasized by the incidence of apical systolic murmurs. Fahr<sup>2</sup> states that it has been estimated that of all children from 6 to 14 years of age, 40 to 70 per cent present apical systolic murmurs, in the second decade of life, 35 per cent of all normal persons manifest it, in the third decade, 22 per cent, in the fourth decade, 19 per cent.

In the literature there are to be found two opposing views on the significance of systolic murmurs unaccompanied by other symptoms. The older one, prominent before World War I, assumed that all sys-

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first sound or by a systolic gallop, in fact, the latter may give the impression of a presystolic murmur

In earlier reports<sup>9, 27 28</sup> I cited instances among naval personnel which affirm the need for accurately evaluating apical systolic murmurs. Early valvular disease was first revealed when these men were stationed in the South Pacific area during 1942. They developed the signs and symptoms of heart failure, they complained of pain, fatigue, and shortness of breath. Their past histories recorded questionable heart murmurs heard by their family physicians, insurance doctors, or the recruiting officers at the time of enlistment, but the murmurs had not been regarded as significant. Other instances of unsuspected early heart disease were found in the course of reexamining men whose health records had been lost in the sinking of ships. More than half of the men gave past histories of rheumatic fever, and many of them experienced recurrences of the disease.

### DIAGNOSIS

Bearing in mind the factors which tend to complicate the diagnosis of apical systolic murmurs, careful examination of the patients should make it possible to establish the nature of a murmur.

*History* As already pointed out, loud apical systolic murmurs occurring in patients who have a history of rheumatic fever is almost certain evidence that disease of the mitral valve exists. Equally significant is a history of an infection by the group "A" *Streptococcus hemolyticus*, since rheumatic heart disease may be associated with infections of this type. In a recent report, Watson, Rothbard, and Swift<sup>29</sup> demonstrated the relationship of scarlet fever to rheumatic fever and rheumatic heart disease, on the basis of this streptococcus.

*Physical examination* In the type of heart disease under discussion, enlargement of the heart is not observed, an apex thrill is not felt, nor is a diastolic murmur routinely audible. The first sound at the apex is loud, as is the second pulmonic sound. The murmur at the apex is loud and prolonged, it begins and is concurrent with the first sound. The presence of a "musical" murmur, a "sea gull" murmur, a "harsh" murmur, or a "constant" murmur, is of additional diagnostic value. If a loud, long murmur has been once heard or reported, or if for any reason there is suspicion of organic heart disease, the patient should be examined again and again in all positions. Hope,<sup>30</sup> as early as 1832, described the

evanescent character of mitral murmurs. The left lateral recumbent position and the sitting position with the patient leaning forward and to the left are the most advantageous. Auscultation after exercise or after inhalation of amyl nitrite is helpful. These maneuvers may elicit not only a loud apical systolic murmur which will persist for some time, but they may also disclose the presence of a diastolic murmur, thereby confirming the diagnosis of mitral valvular disease.

*Phonocardiogram* The phonocardiogram has been found to be a useful diagnostic aid. It may prove that the murmur is prolonged throughout the systole (holosystolic), and it may also disclose an inaudible diastolic murmur.

*Teleroentgenogram and fluoroscopy* In early or incipient (or occult) valvular disease, neither teleroentgenographic nor fluoroscopic study will reveal enlargement of the heart, appearance of the left auricle far over on the right side, and indentation of a barium-filled esophagus. However, these examinations frequently disclose straightening of the left border of the heart, that is, prominence in the region of the pulmonary artery and left auricular appendage. A characteristic sign may be obtained by examining the patient in the left oblique position. It will be seen that the left auricle has begun to enlarge, and that it fills the space under the left main bronchus but does not elevate it. Elevation of the bronchus occurs only with advanced left auricular enlargement.<sup>9 31</sup>

*Electrocardiogram* The electrocardiogram is not of much value in the diagnosis of early mitral disease. However, deformity of the mitral valve may be suspected if there is present right axis deviation of the QRS, a P-wave more than  $2\frac{1}{2}$  mm in amplitude, a P-wave at least 0.10 second in duration, or a well-notched P-wave.<sup>31 32 33</sup>

*Differential Diagnosis* Neurocirculatory asthenia or effort syndrome or "small" heart syndrome and certain deformities of the chest are conditions which most frequently offer problems in differential diagnosis. In the former condition, a systolic thrill may be felt, and a loud apical systolic murmur may be heard concomitantly with a loud first sound at the apex and a loud second pulmonic sound. To add to the difficulty but also to the interest of the problem, the x-ray film will demonstrate a straight left border of the heart and the electrocardiogram may disclose the abnormalities previously described for mitral valvular disease.<sup>9 31 34</sup> However, keeping in mind that a patient with effort syn-



drome exhibits signs that are also present in mitral valve disease, the differentiation can usually be made on the basis of recognized symptoms of neurocirculatory asthenia. Furthermore, a patient with effort syndrome is thin, possesses a low diaphragm with a long, narrow or small heart, he is nervous, has a tremor, complains of dizziness and giddiness, often of severe precordial pain unrelated to effort, and presents symptoms of anxiety neurosis.

### DISCUSSION

Incipient valvular heart disease manifested only by a loud apical systolic murmur is observed more frequently among men in the armed forces than is advanced disease of the mitral valve. This apparently higher incidence during wartime is attributable, of course, to the fact that persons with pronounced signs of mitral valvular disease are not accepted into the armed forces, whereas in civilian life the physician usually sees those patients who seek advice because of the severity of their symptoms. Actual battle conditions will cause the breakdown of a man with early or dormant valvular heart disease who might, in civilian life, live for years—in fact, to old age—without knowledge of his heart defect unless he worked at heavy manual labor or was subjected to unusual emotional strain or entered competitive sports such as football and tennis. In many instances, rheumatic heart disease is discovered only at autopsy or when the patient first develops subacute bacterial endocarditis in middle or in old age.<sup>35</sup> In a study of 100 consecutive autopsies on patients who died of acute coronary artery occlusion,<sup>36</sup> 17 patients were found with definite rheumatic valvular disease, only 8 of whom had had symptoms or knowledge of the disease during life.

Although a history of rheumatic fever or evidence of infection by the group "A" *Streptococcus hemolyticus* is of utmost value as evidence for the organic nature of a loud apical systolic murmur, it should be recalled that 20 to 25 per cent, and perhaps even as many as 50 per cent, of the patients do not give a history of rheumatic fever.

In the evaluation of apical systolic murmurs, the loudness or the intensity of the murmur is of more significance than its transmission. As Levine and Likoff<sup>1</sup> have shown, the louder the murmur, the greater the transmission. In doubtful cases, a phonocardiogram will establish the length of duration of a murmur and will also reveal the presence of any murmur which may not be audible. At the present time, a good portable

stethographic machine is on the market

To be of value as evidence of organic heart disease, it is not enough that exercise produce a systolic murmur at the apex. The murmur must be loud, prolonged, and of some duration. In other words, the loud murmur must persist for a longer period than is to be expected from the effect of exercise alone. Effort, particularly if strenuous, produces murmurs in a healthy person, but these will disappear almost immediately with cessation of the exertion and certainly with the slowing of the heart.

The necessity for repeated examination of all patients in whom there is a question of the significance of a systolic murmur cannot be emphasized too strongly. Examination time and again, in different positions and following exercise, will often be required, because in early cases of valvular heart disease, the murmurs are transient.

One of the most useful indications of beginning mitral valvular disease is to be found by teleroentgenographic and fluoroscopic examinations. The left auricle enlarges to the left and upward before it enlarges posteriorly and to the right, thus producing the prominence in the region of the pulmonary artery and left auricular appendage. The left main bronchus is not yet elevated, nor is the barium-filled esophagus indented, but in the left oblique position the left auricle fills the lung space under the left main bronchus. Grishman, Sussman, and Steinberg<sup>37</sup> believe that the prominence in the region of the pulmonary artery is caused by the pushing up and to the left of this vessel by the enlarging left auricle.

The electrocardiogram, useful in advanced or moderately advanced mitral valve disease, is only occasionally of aid in the type of incipient heart disease under discussion.

Cabot<sup>4</sup> has often been quoted by those who believe that an apical systolic murmur, whatever its character, is not indicative of heart disease unless it is accompanied by other signs of cardiac disease, such as enlargement of the heart, presence of a (diastolic) murmur, or evidence of heart failure. It is my belief that this view proves only that pure mitral insufficiency is rare. A systolic murmur alone is important to the recognition of the early mitral valvular defect—enlargement and diastolic murmurs come later. It is probable, however, that even in early cases, postmortem examination would undoubtedly reveal some anatomical evidence of stenosis.

Although the purpose of this paper has been to prove that a loud apical systolic murmur should be accepted as evidence of organic mitral valvular disease even in the absence of other physical signs, it is not my intention to imply that a patient with this sign should be treated as an invalid. Even in wartime he may be assigned to limited duty without untoward effect, and in civilian life he can carry on practically as well as a normal person, barring undue physical or mental exertion.

### SUMMARY

1 The loud apical systolic murmur unaccompanied by any other sign of valvular heart disease has been discussed. The murmur is evidence of incipient or latent heart disease.

2 Patients with beginning valvular heart disease break down in wartime and also under peacetime conditions if they are exposed to severe or continuous physical exertion or emotional stress.

3 The war presented an unusual opportunity to see cases of this early heart disease, but the lessons learned are applicable to civilian practice.

4 Insurance figures reveal an increased mortality rate among persons whose only sign of heart disease is a loud apical systolic murmur.

5 Certain difficulties are encountered in evaluating apical systolic murmurs, i.e., murmurs vary, they appear and disappear and apparently often regress completely, a history of rheumatic fever may not be obtained in half the cases of organic valvular disease, the problem of differential diagnosis is ever present. The very appreciation of these difficulties facilitates interpretation of the murmur.

6 A history of rheumatic fever or of any disease attributable to the Group "A" *Streptococcus hemolyticus* is corroborative evidence of heart disease.

7 A careful physical examination may uncover physical qualities of the murmur in addition to its loudness, which add to its significance. A loud first sound at the apex, a loud second pulmonic sound, a holosystolic murmur, a "musical" murmur, a "harsh" murmur, a "sea gull" murmur, a "constant" murmur, all lend importance.

8 Repeated examination, in many positions, and after exercise may be necessary. Furthermore, a diastolic murmur may be discovered.

9 Exercise is useful only if a loud or a prolonged systolic murmur results and persists for a longer period than is to be expected from the

effect of the exertion alone. The murmur must remain at least until the heart rate slows.

10 The phonocardiogram is valuable in proving the presence and the duration of the systolic murmur and in demonstrating an unsuspected diastolic murmur.

11 The x-ray film and fluoroscopic examination help in revealing a straightened left border of the heart and, more particularly, filling in by the left auricle of the space under the left main bronchus. This is an early sign of left auricular enlargement and appears long before the esophagus becomes indented or the left auricle moves to the right side of the heart.

12 In the presence of heart failure, there may be no obvious enlargement of the heart in beginning valvular disease.

13 The electrocardiogram is only occasionally of service in early valvular heart disease.

14 In differential diagnosis, the important conditions to bear constantly in mind are (1) effort syndrome or neurocirculatory asthenia (the "small" heart syndrome), (2) the funnel-shaped and the flat chest, and (3) a split first sound. One must also think of hypertension, hyperthyroidism, and anemia in the differential diagnosis.

15 The loudness or intensity of a murmur is more significant than the transmission. The latter depends on the former.

16 Incipient valvular heart disease occurs as frequently in peacetime as in wartime, but under the latter conditions a patient is likely to break down, whereas in civilian life he may live with unsuspected heart disease to a ripe old age. In fact, heart disease may be discovered only at post-mortem examination or when subacute bacterial endocarditis develops. The man or woman in ordinary life will carry on a normal existence provided he or she does not attempt heavy physical labor or work under undue emotional strain. Although loud apical systolic murmurs in early heart disease always have a practical importance, even in wartime the patient may be fit for limited duty.

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SIMON FLEXNER

1863 - 1946

## IN MEMORIAM

## SIMON FLEXNER

**D**R SIMON FLEXNER, Member Emeritus of the Rockefeller Institute for Medical Research, died May 2, 1946. A distinguished and able scientist, he played a very important rôle in the advancement of medical science in this country. Living during what he has called "The Heroic Age of American Medicine," he was one of the leading figures in the period during which medicine in this country advanced from a very inferior position, as regards science, education and practice, to the commanding place it now occupies.

He was born in Louisville, Kentucky, March 25, 1863, and received his preliminary education in the public schools of that city. His father was a druggist, and Simon, after leaving school, became a clerk in his father's store. His mother and father were ambitious for their children, and had high ideals and a great respect for education and learning. They must have had great native ability and were suitably mated, for all their sons later rose to positions of distinction and importance. Simon early showed an enterprising spirit and an interest in what was occurring in the medical world, for even while working in the drug store, he was making sputum examinations for the Louisville doctors, and this only a few years after the tubercle bacillus had been discovered.

After several years in the drug store, he entered the Medical School of the University of Louisville, from which he graduated in 1889, with the degree of M. D. Even in those days of incompetent medical schools in this country, this school was of relatively inferior rank, and it is remarkable that with this scanty and deficient formal education, he could later have become a learned and cultivated man and a leader in the science of medicine.

His education really only commenced when he decided to go to Baltimore to study pathology under Dr. William Welch, who, a few years previously, had been appointed Professor of Pathology in the Johns Hopkins University, and who, at this time, was teaching post-

graduate students in the Johns Hopkins Hospital. At Johns Hopkins, Flexner breathed a new, rare and stimulating atmosphere. During the previous half century, leadership in pathology and medicine had passed to Germany. Great advances in physiology were being made by the pupils of Johannes Muller and especially by Ludwig, and the study of pathology was being actively prosecuted by Virchow, Rokitsansky, Cohnheim and their students. Moreover, the recent advances in bacteriology were opening up wide vistas in knowledge concerning the etiology of the infectious diseases. Notwithstanding the brilliant experimental investigations of Claude Bernard and the discoveries of Pasteur, the most gifted young American students of medicine were being attracted to Germany rather than to France. This was probably due, not only to the ability of the teachers in Germany, but also to the development of the German universities, especially in science, and the stress that was being laid in them on experimental research. Young American students, like Welch and Prudden, came back from Germany bringing with them knowledge of the new techniques in bacteriology and, more important, filled with enthusiasm for promoting further advances on this side of the water. Johns Hopkins, with its relatively large endowment and the high idealism of its founders and promoters, seemed the place of greatest opportunity. As a result, there collected about Welch and the other young professors a group of gifted young men eager to carry on research. None of them responded more readily to the stimulating atmosphere than did Flexner. He had been there but a short time when independently, and unknown to Welch, he carried out an investigation, the results of which were considered worthy of publication. Welch soon recognized Flexner's ability, and when Flexner consulted him about taking his course in bacteriology, Welch replied, "There is no occasion to enter the course, study a problem." During the remainder of his life, Flexner learned by studying problems, and he never was without one. Moreover, he seemed to choose his problems with unerring skill, always selecting them in fields promising a rich harvest, and avoiding working in fields which at the time were unsuited for cultivation.

He was soon (in 1891) appointed a Fellow in Pathology, and he continued to be associated with the Johns Hopkins University and Medical School until 1899. In 1893 the Medical School was opened, and thenceforward he was engaged in teaching as well as research, and he



proved to be a stimulating and capable teacher. During his last year he had the title of Professor of Pathology. This year he was made a member of a commission sent by the University to the Philippine Islands to study the diseases prevailing there. He made a thorough investigation of dysentery, and succeeded in isolating a bacillus which he demonstrated to be the etiologic agent in many of the cases. This organism has since been known as the Flexner bacillus. On his return, he accepted an appointment as Professor of Pathology at the University of Pennsylvania.

But at this time other events were occurring which were to change the course of his career, and also to influence profoundly the course of scientific medicine. Mr. Frederick T. Gates, a layman and an advisor to John D. Rockefeller, became interested in medicine and was impressed by the great poverty of accurate knowledge concerning disease. He decided, "that medicine could hardly hope to become a science until it should be endowed, and qualified men be enabled to give themselves to uninterrupted study and investigation." He persuaded Mr. Rockefeller to make a gift for this purpose, and he consulted Dr. Welch and others in regard to the appointment of a man to head this undertaking. The position was offered to Dr. Flexner. The funds available at first were very moderate and the future seemed uncertain. But Flexner's imagination was aroused and he decided to undertake the new adventure, even at what seemed to be a personal sacrifice.

The first laboratories of the Rockefeller Institute for Medical Research were opened in 1904, and from that time until his death, Dr. Flexner was associated with this institution. He acted as Director until his retirement in 1935, after which the title of Director Emeritus was bestowed upon him. From the beginning, he made it clear that he had no desire to convert the Institute into a Flexner Institute. A few years previously other institutes for medical research had been established in Europe, notably, the Pasteur Institute in Paris and the Institute for Infectious Diseases in Berlin, the latter soon being known as the Koch Institute. Flexner's conception of an institute for medical research was much broader than that of an organization developing around the work of an individual, however great a genius that individual might be. In addition to the laboratories of pathology and bacteriology, where Dr. Flexner's immediate interests were centered, there were laboratories of physiology and pharmacology and of biological chemistry. He saw

that advances in medicine are dependent on advances in the underlying and fundamental sciences. However, in view of Dr Flexner's training, and because of the great interest at the time in pathology, and especially in bacteriology, it is understandable that the first important problem undertaken should concern one of the infectious diseases. At this time an epidemic of cerebro-spinal meningitis was prevailing in New York City, and Dr Flexner and his associates immediately began an investigation of this disease. They succeeded in developing an immune serum, and devised methods for its therapeutic use, that had great value, and has been efficacious in saving many human lives. At the same time, other important contributions were being made in the various laboratories of the Institute.

A few years later, another epidemic occurred in New York, this time due to infantile paralysis. Again Dr Flexner and his associates undertook a very extensive investigation in order to learn the nature of the malady. Among many other important contributions that were made, Dr Flexner showed that the disease could be reproduced in monkeys by the inoculation of material from a fatal human case after this material had been passed through a filter which would remove all bacteria. He thus demonstrated that the infectious agent in this disease is a so-called filterable virus. Later Dr Flexner added much to knowledge concerning other infectious diseases, especially to knowledge concerning sleeping sickness (lethargic encephalitis). He was an able and productive investigator.

But, important as his own scientific discoveries have been, his most important contribution has been the development of the Rockefeller Institute and the influence which he and it have exerted on the advancement of experimental and scientific medicine. Under his direction, the Institute has grown from its very modest beginnings to its present size, with its large resources and large staff of investigators working in a great variety of fields. Vastly more significant than its growth in size, however, is the fact that he has endowed it with the highest ideals of scientific work. Under his direction, the Institute has concerned itself with problems of a fundamental character, and has avoided undertaking studies of a transient and superficial and trifling nature. In order to make the Institute as productive as possible, it was necessary to recognize and support ability and genius wherever found, and in whatever garb. It was also very important to make sure that they were not merely

impudence and folly in disguise To do these things requires even more skill than to make scientific discoveries Time has shown that Dr Flexner was an expert impressario and that he made few mistakes It was important that the workers be given the greatest freedom, but they had to be guided and protected, even against themselves While never a dictator, Dr Flexner was always the director On one occasion, it was suggested by one of the workers, whose previous experience had been in academic life, with frequent committee meetings and formal conferences, that the members of the staff should take a more important part in the management, and a meeting was held for organization At the meeting, it was unanimously agreed that no one except Dr Flexner was capable of heading the organization, and he was elected president The president never called another meeting, and the organization was never heard of again Dr Flexner always consulted with his associates informally before making important appointments or deciding changes in policy, but he felt that scientific investigators should be relieved so far as possible from the details of administration The wider significance of the development of the Rockefeller Institute is shown by the establishment and growth of many other research institutes, both here and abroad, institutes not only for the study of disease, but research institutes covering many fields of human endeavor, even industry and commerce Some of them have been directly patterned after the example of the Rockefeller Institute, all of them have been greatly influenced by the ideas and ideals of Dr Flexner

Less direct, though of very great importance, is the rôle which he has played in the improvement in medical education which has occurred during the period of his scientific life, and in which his brother Abraham has taken so important a part Simon did not have the qualities of a reformer, or an advocate, or a pleader His influence has been exerted largely through example But it is evident that without teachers who were trained in scientific methods, and were imbued with the enthusiasm which is inspired by scientific progress, education, no matter how large the material resources, could not advance very far In transforming the teachers in the medical schools from mere retailers of knowledge into true scientists, Dr Simon Flexner has had great influence As a very influential member of the Rockefeller Foundation, which has contributed so lavishly to the endowment of medical education in this and other countries, he was able to be of very great help in charting the

course along which the advances have taken place. As a member of the Board of Trustees of Johns Hopkins University, he had a direct influence on the conduct of that Medical School.

He has also influenced the practice of medicine, not merely by increasing and improving the armamentarium of the physicians by increasing their available knowledge and supplying new methods, but he has helped to make them accurate, scientific workers. In 1909, a hospital was added to the Institute in order that disease as it occurs under natural conditions could be observed and studied. Largely due to the influence of Dr. Flexner, it was provided that the physicians in the hospital should not only have charge of the treatment of the patients, and observe the superficial characters of disease, but that they themselves should at the same time be actively engaged in investigating the underlying phenomena. Besides making important contributions to knowledge, this hospital has developed many physicians who have later become professors of medicine, here and abroad, and who have carried the spirit of scientific investigation into many medical clinics, and have influenced many students of medicine.

The influence of Dr. Flexner on Public Health has also been of much significance. Through his connection with the Rockefeller Foundation, he was interested in the work of the International Health Division, and when that organization established laboratories for the investigation of problems relating to its work, these laboratories were located in the buildings of the Institute. Dr. Flexner greatly aided in the activities of these laboratories by his support and advice, and they have been instrumental, not only in improving the scientific attitude of those engaged in public health work, but they have made contributions of great practical importance, as, for instance, concerning the nature and prevention of yellow fever. Dr. Flexner was a member of the Public Health Council of New York State from its foundation, and in recent years served as its chairman. He thus exerted an influence on the more immediate and practical problems of public health work. In later years he himself conducted experimental studies concerning the nature of the epidemic occurrence and spread of disease.

In 1903, Dr. Flexner married Helen Whitall Thomas of Baltimore, a sister of Mary Thomas, President of Bryn Mawr University, in which institution Mrs. Flexner had previous to her marriage been a teacher of English. Her knowledge of English literature and her fine taste and

literary ability were undoubtedly of much influence in widening the interest of Dr Flexner in literature and the humanities. He became a cultivated speaker, and his scientific writings have great simplicity, clarity and accuracy. From 1905 to the time of his death, he was the editor of the *Journal of Experimental Medicine*. Under his editorship it maintained the high, almost meticulous, standards of its first editor, Dr Welch. Following his retirement, Dr Flexner, with his son, James, published a biography of Dr Welch, which has great literary excellence, and is not only an authoritative account of his life, but it is a sincere tribute to the man who as long as he lived was Dr Flexner's "guide, councilor and friend."

During the life time of Dr Flexner, knowledge concerning disease has increased at a rate never before equaled. To this advance, the United States has now become probably the largest contributor, whereas previously, it contributed comparatively little. It is, of course, impossible to say for exactly how much of this change Dr Flexner has been responsible. Certain it is that he has been one of the most important figures in this development. With the exception of Dr Welch, probably no single man has played so important a part in the advance of scientific medicine, and with it the improvement in medical education and practice in this country. There is no doubt that the Rockefeller Institute has been of great importance. For this, Dr Flexner is in great part responsible. Although his name is not inscribed over the portal, it is his monument.

RUFUS COLE

*Summary and Recommendations of Report on Planned Parenthood  
Clinics by the Committee on Public Health Relations of  
The New York Academy of Medicine\**

I—SUMMARY

In Greater New York there are above 25 organized places where a woman may apply for contraceptive advice, instruction, and the necessary supplies. These may be classified as follows:

- 1 Special contraceptive hospital clinic departments
- 2 Hospital gynecological clinics
- 3 The Margaret Sanger Research Bureau (Affiliated with the Planned Parenthood Federation of America, Inc.)
- 4 Planned Parenthood Committee of Mothers' Health Centers, and cooperating Maternal Health Centers—Kings County Planned Parenthood Committee, Staten Island Committee for Planned Parenthood, Far Rockaway Mothers' Health Center Committee, and Planned Parenthood Committee of Jamaica, all affiliated with the Planned Parenthood Federation of America, Inc.
- 5 Two independent organizations: The Judson Health Center, and the International Workers Order Birth Control Clinic.

A summary of the organization and work of these clinics and centers is herewith presented:

*Special Contraceptive Hospital Clinic Departments*—There are only 5 hospitals in Greater New York in which contraceptive advice is given in a separate department. These departments are well housed, and their work measures up to fair clinical standards. Considering the great demand for contraceptive advice and the large area from which these hospitals draw patients, the number of women served is very small.

*Hospital Gynecological Clinics*—The hospital gynecological clinics giving contraceptive service have no separate records for contraceptive work. Consequently there is

no way of telling, without going over every record in the clinic, the number of women taken care of, the type and character of the work done, and the results.

In some of the gynecological and post-partum hospital clinics the work is done *sub rosa*, and therefore no records are kept.

*The Margaret Sanger Research Bureau*—This is the best equipped and largest center in Greater New York. It is the leader in the contraceptive work done in the city. It sets the example for all the extramural centers, and a great majority of the physicians now in charge of contraceptive clinics have had their training at the Bureau.

*The Planned Parenthood and Maternal Health Centers*—With the exception of the newly established Harlem Center, these centers are usually located in settlement houses, or in improvised locations, where the facilities for proper type of work are limited. The waiting rooms are crowded, and in some places they are in hallways, without any provision for the patients' comfort. Both new and old patients attend on the same day. Under such a plan, the centers are crowded, and patients who return to obtain new material must very often wait unnecessarily long periods of time. The doctors and nurses are constantly hurried in their work.

*The Judson Health Center and the International Workers Order Birth Control Clinic*—These clinics function independently. Both receive a rather small number of patients. Both have adequate quarters. In one instance the contraceptive clinic is a part of a general health clinic and most of the patients are referred from this clinic. The other is maintained by a labor union and the clientele is largely from among the union members.

*Physicians*—With the exception of the director of the Margaret Sanger Research

\* Approved by the Council of the Academy on Wednesday, March 27, 1946.

Bureau, all the doctors employed in the contraceptive centers are women. The physicians in charge of the Planned Parenthood centers are giving their services for small fees, and many of them are not interested in the underlying medical and social problems. Often, they are not the best physicians obtainable, and their work is frequently superficial. The type of work done at the centers requires a certain amount of teaching ability, tact, and time. To the average patient, the technique of contraception seems strange and complicated, and unless the physician can make herself clearly understood and be patient, the woman may become confused and discouraged. Several of the doctors are foreigners and difficult to understand in ordinary conversation.

*Records*—The forms and charts used in the centers are furnished by the Planned Parenthood Committees. The social history is usually taken by a volunteer, or, in case the volunteer is absent, by the nurse who has a great many other duties to attend to at the same time. Most of the histories are taken either in an open waiting room or in a small partitioned office, no provision is made for privacy. Questions and answers can be heard by those present in the room. This is not conducive to accurate history taking, or to obtaining information which the patient considers confidential. The personal and family histories taken by the volunteers are however fairly complete. The workers are untrained in handling patients and unfamiliar with the basic principles of social service. They render their services gratuitously, and there is no way of controlling the quality of their work or the regularity of their attendance.

The medical histories often are sketchy and incomplete, either because of the constant pressure of new patients or the carelessness of the physician. The marital histories which are classified under general physical examination, receive little attention. The follow-up records seem entirely inadequate and of no scientific value. Furthermore the records are not cross-indexed.

*Examination*—The physical examination usually is limited to a pelvic examination which is fairly adequate. Rarely is a record made of a general physical examination.

As most of the physicians are general practitioners, their diagnosis of pelvic abnormalities leaves much to be desired.

*Referrals*—Whenever an abnormality is found, the patient is referred to her own private physician, if she has one, or to a hospital clinic. No physician is permitted to refer a patient to her own office. Contrary to rumors, there is no evidence that this type of unethical practice is in existence in the Planned Parenthood centers in Greater New York.

*Methods Prescribed*—The procedure followed in all centers consists of the use of coil-spring type diaphragms and jelly. In complicated cases where a regular vaginal diaphragm will not fit, a special diaphragm or cervical cap is fitted.

*Effectiveness of Method*—The information obtained in those hospitals where the follow-up is fairly reliable indicates that the method is effective, but that many of the patients tire of the elaborate preparation. A follow-up in one of the hospital clinics, where only those having serious medical indications were given contraceptive advice and told that pregnancy might endanger their lives showed that only about 70 per cent persevered in the use of the method. 20 to 30 per cent were human failures.

*Administrative Practice*—The trained nurse is the administrative director of the individual center. She admits the patients, supervises the work of volunteers, gives the lectures and demonstrations, sets up the treatment room, takes care of all the supplies, assists the doctor, collects the fees, and sees that everything is safely stored away. In her spare time, she sends out follow-up cards.

*Admission Practice*—Admissions at the extramural centers are made almost entirely by the nurse, and very few applicants are turned away. As far as could be learned, only unmarried women are excluded.

*Fees*—Charges are graduated according to the income and the number of children in the family.

*Follow-up*—In New York City the follow-up consists of sending a letter to the patient who has not returned after six months, and visiting the home of the patient if the letters bring no result. In the Brook-

lyn centers because of the scarcity of nurses, no home visits are made. In all centers, if the patient does not return within a year, the case is considered closed.

In short, the Planned Parenthood centers are trying to do an important and necessary work with limited financial resources and without the proper facilities. Such facilities can best be provided by hospital clinics.

## II—RECOMMENDATIONS

1 The New York Academy of Medicine with its traditional interest in the health and welfare of the family and in problems of human fertility, should assume leadership in the recognition of medically indicated contraception as an integral and essential part of preventive medicine.

2 Contraceptive advice should be given by well-trained physicians, both in their offices and in hospital clinics, only when on the basis of a thorough medical study, they are professionally and morally satisfied that such action is justified. Child-spacing should be recognized as a medical indication.

3 The New York Academy of Medicine should declare itself in favor of including the teaching of indications, and the training in techniques of contraception, in medical college curricula, and of providing facilities for postgraduate education of interns, residents, and other physicians.

4 Inasmuch as family-planning advice is a health service, private physicians and hospitals, as well as the proper health authorities, should assume the responsibility of providing it.

5 When contraceptive services have become a recognized part of hospital service in the city, the Planned Parenthood centers should confine themselves to the education of the public, and all education should be under medical supervision.

6 The educational program of the Planned Parenthood Federation toward fertility should take a positive attitude as well as a negative one. Contraceptive advice in the centers operated by Planned Parenthood organizations should not be given to anyone who may apply for it, but every effort should be made to analyze each individual situation and to urge parenthood strongly, where the conditions warrant it.

7 Until such time as the hospital clinics take over contraceptive clinic service, the Planned Parenthood organizations should continue to maintain contraceptive centers which conform to standards set up for licensure of dispensaries by the State Board of Social Welfare, and The New York Academy of Medicine should strongly urge upon that Board that these centers be licensed, because they are an important part of preventive medicine and because they cannot be otherwise controlled.

8 Centers so licensed should conform to the following criteria:

a They should have adequate financial support to provide good service and proper staff.

b Only physicians well trained in this special work and interested in the medical objectives of contraception should be employed.

c Only nurses who are interested in contraceptive services as a part of maternal health, and who have an understanding of public health and social service procedures, should be employed.

d New cases should be accepted by appointment only, and the number of patients limited, so that the physician and nurse may give the attention each requires. The optimum patient load per physician and nurse should be determined and maintained. Clinics should be held at hours most convenient to the patients.

e New patients should be given a general physical examination at the centers, or elsewhere if this is impossible there, and all the findings should be recorded. Adequate pelvic examinations should be made at the centers.

f The patient's reasons for requesting contraceptive advice should be investigated by the physician and clearly stated on the chart, together with the doctor's reasons for giving such services.

g Patients who seem to have difficulty with the recommended method of contraception or who find it too complicated, should be given some simpler method, which, while not so effective, would probably be used more consistently for a longer period.

h The clinic physician should be trained to look for and recognize abnormalities and



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BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



NOVEMBER 1946

OPENING ADDRESS

*Nineteenth Graduate Fortnight*

GEORGE BAEHR

President The New York Academy of Medicine

THE Graduate Fortnights were established by the Academy in 1928 upon the recommendation of its Committee on Medical Education in appreciation of the periodic need by all practicing physicians for an intensive review of recent advances in the major branches of medicine. Each year a new subject is selected for the theme of the Fortnight. The special field is covered completely within that period by a combined program of morning, afternoon and evening exercises consisting of lectures, demonstrations, exhibits, hospital clinics, seminars and round table discussions. The entire medical profession is eligible to participate. As lecturers and discussion leaders, the Academy assembles the most outstanding authorities in the country.

The scientific exhibits of the Fortnight represent the contributions of many medical schools, teaching hospitals and research laboratories. This year an attempt has been made to group the exhibits according to subject matter rather than by participating institutions, so as to take the most complete advantage of their educational values. It would be

\* Given October 7, 1946 at the opening of the Fortnight

## MEDICAL GENETICS AND PUBLIC HEALTH

*The Twenty First Hermann M. Biggs Memorial Lecture*

LAURENCE H. SNYDER

Professor of Medical Genetics College of Medicine and Chairman of the Department of Zoology and Entomology the Ohio State University

THE field of public health has always been noted for its ability to put to practical use the basic discoveries of the various sciences which have had something to contribute to public welfare. With medicine as a core, public health has enlisted the aid and support of bacteriology, sanitary engineering, statistics, entomology, veterinary medicine, sociology and other pertinent disciplines. Following the early use of primitive measures of sanitation, the discovery of microbes opened a new and important phase of public health, leading to the control of many infectious diseases and the inspection and supervision of food and water supplies. More recently the activities in this field have widened to include such things as city planning, zoning, building of cheap transportation and recreational areas, provision of labor-saving devices and safety measures, and the general improvement of economic conditions.

These things, which have done so much for human progress, have been almost entirely aimed at the control of unfavorable conditions of the environment. Today most of these conditions are well under control, or at least could be if enough people wanted them controlled. There remain, however, a number of stumbling blocks to human health, the basic cause of which is genetic. As the infectious and nutritional diseases are conquered one by one, the genetic anomalies and diatheses become of greater relative importance. And just as the medical bacteriologist pointed the way to the control of infectious diseases, and the biochemist to the regulation of nutritional disorders, so the medical geneticist now holds out hope for the understanding, and thus the eventual control, of the genetic dyscrasias.

From the basic study of the principles of heredity there is emerging a new science, medical genetics, which applies these principles specifi-

cally to man. From careful research in the laboratory, in hospitals, and in homes and communities, a large amount of exact information has been gathered concerning the part that genetic variability plays in the production of human traits. Just as public health measures have depended for their success not only upon the training of specialists in the field, but also upon the education of the public, so also the newest handmaiden of public health, medical genetics, is developing both specialized and public interest. So important has our knowledge of human heredity become that courses in medical genetics are becoming standard units of the medical curriculum. Popular interest has dictated the appearance of books and magazine articles on human inheritance, and public lectures such as this one are being presented under a wide variety of auspices.

The precision of our knowledge has now reached the point where definite practical applications are available and in use. These include first, prevention, that is, the instituting of preventive measures against certain diseases and abnormalities, on the basis of specific genetic backgrounds, second, diagnosis, on the basis of genetic data, of conditions difficult to identify by other means, third, genetic prognosis, that is, the furnishing of genetic advice in prospective marriages and prospective families, and fourth, the determination of non-paternity and other medico-legal and medical problems, on the basis of the various blood agglutinogens.

Let us first consider prevention. Of all the applications of medical genetics, the one potentially most valuable is in the field of preventive medicine. It is becoming more and more feasible to prevent, in the relatives of persons with genetic conditions, the appearance of the abnormality or disease. The procedure is to examine the relatives of an affected patient by means of suitable laboratory tests, in search of the early pre-clinical or laboratory signs of the trait. When these are discovered, preventive measures are instituted.

Let me cite some examples from my own experience. At the Ohio State University I work in close association with the men in the departments of medicine and surgery. One of the most brilliant and certain applications of genetic facts to prevention has received much of its impetus from my colleagues in these departments, Doctors Doan and Curtis. I refer to the prophylactic removal of the spleen in congenital hemolytic icterus. In this disease the clinical manifestations are jaundice and marked anemia, sometimes developing as an acute fatal hemoclastic

crisis if permitted to remain untreated. The condition is the result of a dominant hereditary factor, but the clinical symptoms are not always expressed in those who inherit the factor. One or another of the laboratory stigmata is, however, always present if appropriate laboratory examinations are made. These signs include a relatively high reticulocytosis for the degree of anemia, microspherocytosis (rarely macrocytosis), increased fragility in hypotonic solutions of sodium chloride, increased icterus index, and enlarged spleen.

Where one or a combination of these signs is found in a relative of a patient with clinical activity, the spleen should be removed in the potential patient as a prophylactic measure. When it is remembered that such ordinarily minor events as an infection or a broken bone, or physiologic pregnancy in the female, may precipitate a hemoclastic crisis capable of resulting in death, the value and even the urgency of preventive splenectomy are apparent.

In connection with my University duties I teach a course in medical genetics to the medical students. It is my custom at the appropriate point in the course to have presented to the class a family in which hemolytic icterus exists. Recently I called Dr. Doan and asked if he could provide a case on a designated date. He assured me that there would undoubtedly be a case in the hospital at that time.

About a year previously, a man had been operated on for hemolytic icterus, and as is our custom, his children had been called in and examined. Two of his four sons showed the early laboratory signs of the inherited trait, and were advised to have their spleens removed as a prophylactic measure. One agreed, and his spleen was successfully removed, the other refused.

The day before my class period, Dr. Doan called and said that a boy with severe hemolytic icterus in hemoclastic crisis was being sent into the hospital, and would probably serve for presentation the next day. When the hour for the class arrived, however, Dr. Doan appeared without the patient. It had been the boy who a year earlier had refused preventive splenectomy. He arrived in extremis and lived just long enough to say, "I guess I waited too long to have my spleen removed." And he had. He could have been saved by elective prophylactic surgery on purely genetic grounds.

Another example of the genetic application of preventive measures is furnished by an anomaly known as xanthoma tuberosum. It is a stor-

age disease, a lipoidosis. Like hemolytic icterus, it has both clinical symptoms and pre-clinical laboratory signs. The visible symptoms are characteristic nodules and tumors of the tendons and joints. The laboratory signs consist of increases in the blood cholesterol and cholesterol esters. The increases may be as much as to reach 1500 mg per cent, as compared with a normal blood cholesterol of 150-300 mg per cent. The condition may progress to cardiovascular involvement and sudden death.

Since the hypercholesterolemia is transmitted on the basis of a dominant hereditary factor, and since this may be detected by appropriate laboratory tests long before the appearance of visible tumors or nodules, it may profitably be searched for in the relatives of patients with clinical manifestations. Where found, preventive dietary and other appropriate measures may be instituted, thus helping to preclude heart involvement and premature death.

These are just two examples of many that could be cited. It might be argued by the uninitiated that such preventive measures could be invoked without any knowledge of genetics, and so they could, were it possible to examine everyone in the world for every potential disease and anomaly that he might have. Obviously this is not feasible, so that it becomes imperative to do the feasible thing, which is to search for laboratory and pre-clinical stigmata in the places where they are most likely to be found, namely, in the relatives of those patients who have clinically manifested genetic conditions.

Instances like those described, involving dominant genes, provide the most striking opportunities for the application of preventive measures on genetic grounds, since the incidence of affected relatives in cases of dominant heredity is high. A dominant gene is one which produces its effect whether it is present upon both or upon only one of the chromosomes of the pair concerned. A recessive gene, on the other hand, is one which must be present upon both chromosomes of the pair in order to produce its effect. Genes occur in alternative pairs, the two members of a pair being called *alleles*. Obviously if one allele of the pair is dominant, the other must be recessive. Dominant genes are usually symbolized by capital letters, their recessive alleles by the corresponding lower case letters. Thus we may represent the dominant gene resulting in hemolytic icterus by *I*, and its recessive allele for normal activity of the spleen and hematopoietic system by *i*. Then *II* and *Ii* will be the



physicians whom he consulted were unable to give him any relief. One evening he made a social call upon a distinguished neurologist who happened to be a personal friend, and in the course of the evening hesitatingly mentioned this corn which would not get better, apologizing for bringing such a small matter to the attention of a specialist. To the man's amusement the neurologist asked for an X-ray of his lumbar spine. He did this because he had formerly treated the man's two brothers for marked trophic lesions which were the result of spina bifida. Sure enough, in this patient an occult spina bifida was found, and was shown to be the cause of the ulceration.

Not only may diagnoses sometimes be made more readily through the use of genetic backgrounds, but they may often be made earlier than would otherwise be possible. A man 54 years of age was operated on for well developed gastric carcinoma on the lesser curvature, one inch from the pylorus. His 52 year old brother, though having no symptoms, was disturbed by the presence of cancer in the family. The physician suggested that the appropriate tests be run on the brother. They were made, and an identical gastric cancer was found to be developing, one inch from the pylorus. Soon the brothers were in adjoining hospital beds, but the operation on the second brother was performed much earlier than would have been otherwise possible.

The third practical application of medical genetics to public health is our increasing ability to give accurate genetic advice to families. As a result of college courses in genetics, and of popular books and magazine articles on heredity, the well-read layman is rapidly learning that it is possible to get information about the possibility of the appearance in his children of a trait that has previously occurred in the family. Parents and prospective parents are rightfully concerned about these things. Sometimes the question concerns a wanted character such as blonde hair or musical ability. More often it involves an unwanted trait such as club foot, achondroplasia, or mental deficiency.

Before attempting to answer such a question the physician must ascertain several important facts. He must first accurately identify the trait, since minor variations may represent different genetic factors involved. The ease of identification varies. Club foot is readily recognized, while border-line mental deficiency may be difficult of analysis.

When the trait is accurately identified or diagnosed, the literature on human and medical genetics must be searched for recorded instances of

the hereditary mechanism involved. Particular care must be taken to note what variations in the expression of the trait have been recorded within families, what the ages of onset have been, and with what regularity the character may have appeared within families.

It is then necessary to chart the family history of the person seeking advice, and to compare his pedigree with those recorded in the literature or in the files of the physician himself, noting similarities and differences in symptoms, age of onset, and type of transmission.

Finally the possible relations of the anomaly or disease to the environment must be evaluated, and the probable environment in which the trait will develop if it appears in this family must be specified.

With all the above facts in hand it is frequently possible to make a reasonable prognosis. Let me again draw some instances from personal experience.

Within the past year I have been consulted by two families on the question of peroneal atrophy. In one case the father suffered from the disability and wished to know the possibility of its appearance in his children. He had noticed beginning lameness in his late twenties, and at forty he showed pes cavus and atrophy of the hands. He was an only child, and he remembered his mother as being moderately crippled. The late onset and moderate involvement are characteristic of the dominant form, and it was thus possible to predict that about half his children of both sexes would show the trait.

In the other instance the parents were unaffected, but their oldest child, a boy of twelve, was severely crippled. He had begun to have trouble walking at about five years of age, and the atrophy had developed rapidly. Their other children were two girls, aged seven and two, respectively. The parents wanted to know the chances of the two girls developing the atrophy, and whether or not any of these children could transmit the trait.

The onset during the first decade and the rapid crippling are characteristic of the recessive form of peroneal atrophy. In the case of recessive traits, it will be recalled, the gene must be present on both chromosomes of the pair in order that the trait be expressed. This means that it must have been inherited from both parents. In this case, since both parents were unaffected, they must have been heterozygous. In rare recessive traits, it will be unusual to find both parents heterozygous by chance. The situation is much more likely to occur, however, when the

parents are related, since, if one is heterozygous for a trait, the other, being a relative, is likely to carry the same gene. In the family under discussion, inquiry revealed that the parents were first cousins.

It was thus possible to tell the parents that any child of theirs has one chance in four of becoming crippled. Moreover, the normal children have two chances in three of carrying the gene. Even if one of them carries the gene in heterozygous form, however, it will not result in affected children unless she marries a man who is likewise heterozygous.

The foregoing cases illustrate the fact that variations in onset and severity within a trait are often the result of different genic complexes. Conversely, the discovery of various genetic bases for what is apparently a single clinical entity can lead to important clinical distinctions which may even require different therapies. In devious ways is medical genetics making its importance felt in clinical medicine and public health.

Other examples of variations in onset and severity dependent upon different genes are to be found in epidermolysis bullosa and in retinitis pigmentosa.

Recently I was asked to advise a couple with three sons and two daughters. Two of the sons, aged nine and eleven, suffered from pseudohypertrophic muscular dystrophy. A brother of the mother had died of the disease at the age of fourteen. The parents were well aware of the hopeless prognosis for the two crippled boys, but wanted information on the chances of the reappearance of the trait if the normal boy and the two normal girls should marry.

The abnormality in this case is the result of a sex-linked gene, that is, a gene carried on the X-chromosome. Since the gene is recessive, it must be on both X-chromosomes of a woman to express itself, but due to the fact that the boys having this defect usually die before reproductive age, there is little or no chance for a girl to get the defective gene from her father. This type of dystrophy is therefore confined to boys. The chromosome complex of a male includes an X- and a Y- chromosome in place of two X-chromosomes in a female. The Y-chromosome carries no genes of this sex-linked type, so that if a boy inherits the gene for dystrophy on the X-chromosome from his mother, the Y-chromosome from his father will not contribute any gene to counteract or dominate over the defective gene, which can therefore express itself.

If we represent the gene for normal muscle development by  $D$ , and the gene for dystrophy by  $d$ , boys may be either of two genotypes,  $DY$

(normal) and  $dY$  (crippled) Girls will ordinarily be one of two genotypes,  $DD$  and  $Dd$ , both unaffected The genotype  $dd$  (dystrophic female) can obviously not occur as long as the crippled boys die before reaching reproductive age

The defective gene is thus carried along in the population by some of the normal girls in the dystrophic families In the family under discussion the parents were obviously  $DY$  (father) and  $Dd$  (mother) All the boys received the Y-chromosome from the father, but had an even chance of receiving  $D$  or  $d$  on the X-chromosome from the mother The two crippled boys, of course, received  $d$  and were thus  $dY$  The normal brother, who was fourteen years of age, obviously received  $D$  and was  $DY$  It was thus possible to state definitely that he may marry with impunity, since he can not possibly transmit the gene

The daughters, on the other hand, both received  $D$  on the X-chromosome from the father Although they were only three and five years old, respectively, it is certain that they will be unaffected However, they have an even chance that they carry the defective gene from the mother Thus the chances that they may bear crippled sons are fifty-fifty, regardless of whom they marry

Not long ago I was consulted by a young couple who had an infant son suffering from an affliction of the skin in which blebs and blisters appeared wherever the skin was subject to friction The blisters occurred not only on the skin itself, but in the mouth, nose and throat The child had no nails and practically no teeth, and was a mass of raw flesh The diagnosis was made of epidermolysis bullosa dystrophica The prognosis is bad The parents were frantic, and demanded to know whether further children would show the defect

This type of epidermolysis is known to be the result of still another kind of gene, an incompletely sex-linked gene Such genes are located on the homologous regions of the X- and Y-chromosomes These chromosomes are complex, and recent work by Koller<sup>3</sup> has shown that they consist of three portions, as follows First, there is a region of the X-chromosome homologous with a corresponding region of the Y-chromosome, the two parts synapsing during meiosis and forming chiasmata Second, there is a part of the X-chromosome not homologous with any part of the Y-chromosome, and third, there is a portion of the Y-chromosome not homologous with any portion of the X-chromosome The non-homologous regions do not undergo synapsis during meiosis

Genes are known to be located in each of these three regions, and all such genes will be in one way or another associated with sex in their inheritance. Those located on the non-homologous portion of the X-chromosome are called sex-linked, and will be inherited in the manner just described for pseudohypertrophic muscular dystrophy. Genes located on the non-homologous region of the Y-chromosome will be confined to men, and will produce their characteristics only in men. Such traits as *ichthyosis hystrix gravior* and *keratoma dissipatum* are of this nature.

Genes located on the homologous parts of the X- and Y-chromosomes are known as incompletely sex-linked genes, and their transmission is peculiar. About half the families in which the father carries the gene will contain more affected sons and unaffected daughters than would be expected in ordinary inheritance, while the other half will contain more affected daughters and unaffected sons than would be expected. The extent of the discrepancy will depend on the precise location of the gene on the chromosome. The location can be accurately determined by modern genetic methods.

The gene for epidermolysis bullosa of the recessive type is, then, incompletely sex-linked, and located about 20 units distant from the junction of the homologous and non-homologous portions of the sex chromosomes. Since the affected child in the family was a boy, this probably represents a non-crossover, and other affected children in the family will probably be boys. Specifically, another boy in this family would have two chances in five of being affected, whereas a girl would have but one chance in ten of showing the affliction.

The foregoing examples of genetic prognosis are all instances in which sufficient information on the mode of inheritance of the abnormality was available to make accurate predictions possible. Unfortunately, complete genetic data are not equally at hand in all inherent anomalies, and such explicit information can not always be given. There is crying need for more and more research along these lines.

The fourth practical application of medical genetics includes the medico-legal and other medical outcomes of our knowledge of the inheritance of the human blood agglutinogens. It is like carrying coals to Newcastle to speak of the blood groups to a New York audience. This is the place where Dr. Landsteiner, the discoverer of the blood groups, did so much of his work, where he and Dr. Levine worked out antigens

M and N, and where Dr Wiener is even now continuing his remarkable work on the Rh factors. Nevertheless, any discussion of medical genetics and public health would be very incomplete without at least a reference to the subject.

More than twenty years ago I spoke in New York on the inheritance of the blood groups. At that time we knew of four groups, and I thought I had a good deal to say about them. Today we deal with 3200 groups, and the number will probably soon exceed 8000 by virtue of several new antigens which are even now in the process of description.

It will be recalled, then, that in the early days of this century Landsteiner showed that when the erythrocytes of one person were mixed with the serum of another person, agglutination might occur. The reaction took place only in certain mixtures of cells and sera. It was obviously an antigen-antibody reaction, the antigen being located in the erythrocytes, the antibody in the serum. Further work revealed the fact that there were really two antigens occurring in human erythrocytes. These were named A and B. As a result it was possible to distinguish four sorts of individuals: those containing antigen A in their cells (hence spoken of as belonging to group A), those having antigen B (group B), those having both antigens (group AB), and those possessing neither antigen (group O).

A reciprocal relationship exists between antigens A and B and their corresponding antibodies, since each person has either antigen A or the antibody against A, and either antigen B or the antibody against B. Thus there occur in various human bloods natural or "normal" antibodies against A and B.

The most obvious application of this discovery was to blood transfusion, since it would be unwise to transfuse red cells into a person whose plasma would immediately clump the cells. Before any transfusion of whole blood or erythrocytes, the blood groups of donor and recipient must be determined, so that compatible blood may be given.

We were immediately intrigued by the fact that here was a means of distinguishing four kinds of people, and in our laboratory, and those of other investigators, researches were quickly undertaken to determine how the blood groups were inherited. Studies of large numbers of families have disclosed the fact that antigen A is inherited on the basis of a dominant gene. Antigen B is the result of another dominant gene, an allele of the first, and a third allele in the series results in no antigen at

all Consequently antigen A never occurs in a child's blood unless it occurred in the blood of at least one of the parents Similarly, antigen B never appears in a child's blood unless it was present in the blood of at least one of the parents

Although these discoveries seemed at first only of academic interest, they proved soon to be of practical importance as well Cases of disputed paternity, for example, may be settled from data such as these If a child, for instance, is of group A, and the mother is of group O, then we know that the antigen A in the child must have come from the father If the alleged father should be of group B or of group O, we can state definitely that he is not the true father of the child

Following the first world war the intensive study of blood grouping phenomena was undertaken on a large scale One of the outcomes of these researches was the demonstration that antigen A occurs in several detectable subtypes, now named  $A^1$ ,  $A^2$  and  $A^3$  It is thus possible to classify people into eight different groups, namely O,  $A^1$   $A^2$   $A^3$ , B,  $A^1$ B,  $A^2$ B, and  $A^3$ B

Another outcome of blood grouping research was the demonstration that antigens A and B exist in two different chemical forms water-soluble and alcohol-soluble Thus individuals of groups A, B and AB may produce water-soluble antigens, in which the antigens are found not only in the cells but in the body fluids such as the saliva, milk, tears and urine On the other hand, they may produce the antigens in alcohol-soluble form, in which case they will be restricted to the cells

Those persons having water-soluble antigens have been named "secreters," while those whose antigens are not soluble in water are called "non-secreters" By means of special anti-O sera, even individuals of group O can be classified into these two groups

The "secreting" ability is the result of a dominant factor, the "non-secreting" propensity being due to its recessive allele Thus these factors may be added to the armamentarium for medico-legal use Also they double the number of recognizable blood groups Since any one of the eight A-B groups may be either a secretor or a non-secretor, there are  $8 \times 2$ , or 16 groups recognizable in this way

The discovery of antigens A and B resulted from the presence in human sera of normal antibodies against them On the assumption that there might be in human erythrocytes other antigens for which no normal antibodies existed, Landsteiner and Levine injected human cells into

rabbits. When the resulting immune sera were exhausted with appropriate human erythrocytes, the sera still selectively agglutinated other samples of human red cells. It was apparent that the rabbits had produced a specific antibody against a human agglutinin not previously recognized. As a matter of fact, several agglutinins were found by this technique.

Two of the new agglutinins were named M and N. They proved to be related in such a way that a person might have M in his cells (type M), or N (type N), or both (type MN). No one lacking both M and N has been found. Through genetic studies it has been demonstrated in our laboratory and others that these antigens, like A and B, are the result of dominant genes, and consequently never appear in a child's blood unless present in the blood of at least one of the parents.<sup>4</sup> Moreover antigen N, like antigen A, can be subdivided into identifiable types. We recognize  $N^1$  and  $N^2$ , so that there are five types in the M-N series, namely M,  $N^1$ ,  $N^2$ ,  $MN^1$  and  $MN^2$ . Since any one of these five could be any one of the sixteen AB groups, there are  $5 \times 16$ , or 80 different groups detectable in these two series.

In addition to lacking normal antibodies, M and N have proved to be only very weakly antigenic to human beings. They are thus unimportant in blood transfusion, even in multiple transfusions. They can be used, however, as additional criteria in cases of disputed paternity.

In the course of the injection experiments carried out by Landsteiner and Levine, still another antigen lacking normal antibodies was found. It was less satisfactory to use than antigens M and N, since potent sera were difficult to obtain and standardize, and the reactions were weak and variable. The antigen was named P, and later work has resulted in more satisfactory means of detection. For one thing, certain animals have been found to be good sources of normal anti-P serum, particularly pigs.

Genetic studies reveal that antigen P, like the others mentioned, is the result of a dominant factor. Moreover it likewise occurs in two detectable subtypes,  $P^1$  and  $P^2$ , so that with the appropriate antisera four kinds of persons can be distinguished, namely  $P^1$ ,  $P^2$ ,  $P^1P^2$  and P-.

In the combined A-B, M-N and S series there were 80 different classifications of human blood. Since the P factors are independent of the others, any one of the 80 could be any one of the 4 types in the P series, thus making altogether  $80 \times 4$ , or 320 different groups.

Continued attempts at discovering more antigens by injection of



human blood into animals gave disappointing results Landsteiner and Wiener therefore approached the problem from a different angle They injected blood from the monkey, *Macacus rhesus*, into rabbits The immunized rabbit serum was found to agglutinate human cells selectively, thus identifying still another human agglutinin which proved to be independent of all those previously studied Using the first two letters of rhesus, the antigen was named Rh Eighty-five per cent of white Americans proved to have the new antigen, and these persons are spoken of as Rh+ The other fifteen per cent, lacking the antigen, are called Rh—

Genetic studies of the new antigen revealed the fact that it, too, is inherited on the basis of a dominant gene, and may therefore be used with the other antigens in medico-legal applications

There are apparently no normal antibodies against antigen Rh in human plasmas In this regard the situation is similar to that in antigens M and N There is a difference, however, in regard to antigenicity, since Rh is antigenic to man This fact leads to several extremely important clinical applications

In blood transfusions it is essential to transfuse only Rh— blood into an Rh— person, since repeated injections of Rh+ blood may result in immunization of the recipient with hemolytic reactions of increasing severity<sup>5</sup>

Not only is the Rh agglutinin antigenic to man, but it may pass from the circulation of an embryo through the placenta into the mother's circulation, and immunize the mother if she is Rh negative This fact led to the discovery of the cause of erythroblastosis, which had long been known to run in families, but which had never fitted into any clear genetic picture

Even before the discovery by Landsteiner and Wiener of the Rh antigen, Levine and Stetson<sup>6</sup> postulated such a factor capable of immunizing a mother They found an atypical agglutinin in the blood of the mother of a macerated fetus When the Rh factor was announced the following year, it proved to be the immunizing agent postulated by Levine and Stetson In 1941 Levine, Katzin and Burnham<sup>7</sup> demonstrated that the Rh antigen is indeed the primary cause of erythroblastosis, accounting for more than 90 per cent of the cases Recent work of Wiener and his coworkers has established the fact that the other 10 per cent are also due to immunization reactions, either the result of the production

of univalent Rh antibodies instead of the usual bivalent agglutinins, or in occasional cases the result of antigens A and B

In nearly all cases of erythroblastosis the mother is Rh—, the fetus Rh+ The antigen in the fetus was, of course, inherited from the father, and some of it has passed through the placenta into the circulation of the mother, immunizing the mother The maternal immune antibody, which can be demonstrated in the mothers of erythroblastotic infants, has then passed back into the fetus, damaging the erythrocytes The result is hemolytic jaundice or fetal hydrops or macerated fetus, the well recognized symptoms of erythroblastosis While the agglutination of red cells is a demonstrable test tube reaction, the end result in the fetal circulation is most probably hemolysis

As a rule the first Rh+ pregnancy of an Rh— mother serves merely to set up the immunization, while a second or later Rh+ embryo stimulates the further rapid production of antibodies, and is itself affected Occasionally, however, a woman produces antibodies so quickly and strongly that even the first Rh+ embryo may be affected We have some evidence in our laboratory that these affected first-born show gross abnormalities, including spina bifida Within the past year we have seen several such cases, and these will shortly be published

Of course, if an Rh—woman has received a transfusion of Rh+ blood previous to her first pregnancy, she may already have been immunized, and the first Rh+ fetus she carries may then be affected in the usual manner On the other hand, some women appear to produce antibodies so slowly that several Rh+ fetuses are required before one shows the effect of the immunization

Although the original source of anti-Rh serum was immunized rabbits, and later immunized guinea-pigs, it was soon apparent that the serum from mothers of erythroblastotic infants was the best source of test antibodies Nowadays such mothers furnish practically all the available test sera The study of such sera has resulted in the discovery of several types of anti-Rh antibodies, making possible the identification of corresponding new Rh antigens, and the classification of still more kinds of persons

Not long after the discovery of the original Rh agglutinin, Wiener<sup>8</sup> found a human immune serum which agglutinated only 70 per cent of human bloods instead of 85 per cent The new agglutinin identified another Rh antigen, similar to the first The original antigen is now called

TABLE I

<i>Types</i>	<i>Observed Frequency</i>	<i>Genotypes</i>	<i>Theoretical Frequency</i>	<i>Anti Rh<sup>o</sup> 85</i>	<i>Anti Rh' 70</i>	<i>Anti Rh'' 52</i>	<i>(Anti Hr<sup>o</sup>) 63</i>	<i>Anti Hr' 80</i>	<i>Anti Hr'' 57</i>
Rh <sup>o</sup>	024	Rh <sup>o</sup> Rh <sup>o</sup> Rh <sup>o</sup> rh	001024 02336	+	—	—	—	+	+
Rh <sup>o</sup> '	543	Rh <sup>o</sup> ' Rh <sup>o</sup> ' Rh <sup>o</sup> ' Rh' Rh <sup>o</sup> ' Rh <sup>o</sup> Rh <sup>o</sup> ' rh Rh <sup>o</sup> Rh'	187489 011258 027712 316084 000832	+	+	—	—	—	+
Rh <sup>o</sup> "	137	Rh <sup>o</sup> " Rh <sup>o</sup> " Rh <sup>o</sup> " Rh'' Rh <sup>o</sup> " Rh <sup>o</sup> Rh <sup>o</sup> " rh Rh <sup>o</sup> Rh''	021025 00087 00928 10585 000192	+	—	+	—	+	—
Rh <sup>o</sup> ' "	132	Rh <sup>o</sup> ' Rh <sup>o</sup> " Rh <sup>o</sup> ' Rh'' Rh <sup>o</sup> " Rh'	12557 002598 00377	+	+	+	—	+	+
Rh'	005	Rh' Rh' Rh' rh	000169 00499	—	+	—	+	—	+
Rh''	002	Rh'' Rh'' Rh'' rh	000009 00219	—	—	+	+	+	—
Rh' "	000	Rh' Rh''	000078	—	+	+	+	+	+
Rh—	133	rh rh	133225	—	—	—	+	+	+

The genetic basis of the Rh-Hr blood types The theoretical genotype frequencies were derived in my laboratory from the proportions of the Rh types as recorded by Wiener It should be noted that anti Hr<sup>o</sup> has been postulated but not yet described

Rh<sup>o</sup> (or Rh<sub>0</sub>) and the new one is known as Rh' Soon afterward Levine<sup>o</sup> described an immune serum which contained antibodies against both antigens, and agglutinated about 87 per cent of human bloods

Still later Wiener<sup>s</sup> described a third kind of human immune serum which contained a new agglutinin, related to the other two, but reacting with only 32 per cent of human bloods The new antigen identified by this antibody has been named Rh'' Individual persons may have any one of these antigens in their erythrocytes, or any combination of them, or none at all Thus with the appropriate antisera anyone may be placed

in one of eight Rh types, as follows Rh<sup>o</sup>, Rh', Rh'', Rh<sup>o</sup>', Rh<sup>o</sup>'', Rh''', Rh<sup>o</sup>''' and Rh-. The last type is Rh negative, the others are all Rh positive, for one or more of the Rh antigens

Based on the blood groups in the A-B, M-N, S and P series, we have, it will be recalled, 320 types. Since any one of these 320 could be any one of the eight Rh types, we can now distinguish  $8 \times 320$ , or 2560 blood groups altogether

Most recently it has been observed that corresponding to each Rh factor there is a reciprocally related antigen which has been named Hr<sup>10</sup>. Hr is related to Rh in the same way that M is to N, so that a person homozygous for any Rh gene is negative for the corresponding Hr antigen, and vice versa. Corresponding to the three antigens Rh<sup>o</sup>, Rh' and Rh'', three Hr factors, Hr<sup>o</sup>, Hr' and Hr'' are postulated. Hr' and Hr'' have already been described, Hr<sup>o</sup> will doubtless soon be discovered and delineated.

The addition of the Hr antigens to the list makes it possible to break each of the eight Rh types into further subdivisions (Table I). Using anti-Hr' serum, for example, we may now classify Rh<sup>o</sup>' blood into positive for Rh<sup>o</sup>' but negative for Hr', and positive for Rh<sup>o</sup>' and positive for Hr'. Interestingly enough, in most cases this difference will distinguish homozygous individuals from heterozygous individuals, as may be seen from the table, and is thus of importance in genetic prognosis in families in which erythroblastosis has occurred.

Antisera against Hr' are now available, and make it possible to readily distinguish ten Rh blood types instead of eight. Going back to the 320 types classifiable on the basis of A, B, M, N, S and P, and realizing that any of the 320 could be any one of the ten Rh-Hr types, we have now 3200 different blood groups. When antisera against Hr<sup>o</sup> and Hr'' become available in quantity, it will be possible to distinguish 27 Rh-Hr types, and thus  $27 \times 320$ , or 8640 blood groups altogether.

The different genes involved in the production of these diverse antigens occur in varying frequencies from population to population, and herein lies another whole field of research. In any population some of the alleles will be fairly common, others rather rare. Nevertheless, it would be possible for me to take a drop of blood from each one of you in the audience tonight, and with the aid of the proper sera, to place each one of you in one of these thousands of blood groups. It would be surprising if any two of you were to fall into the same group. Then

five years later I could return here, gather you together, take another drop of blood from each of you, and, without knowing the source of the samples of blood, assign each sample to the proper person by referring to my previous list, except, of course, for such duplications of blood group as might exist among you

Returning to erythroblastosis, the question arises as to how often by chance an Rh- woman will marry an Rh+ man and produce an Rh+ child who might thus be affected. This problem, like all the problems involved in the Rh types, is one of medical genetics, and can be solved only by medical genetic methods. Its solution has led to some remarkable new concepts of Rh immunization. Without going into the mathematical methods of gene-frequency analysis, let me say only that we would expect in a population such as ours that 23.8 per cent of all children born will have one or another Rh antigen which the mother does not have.

If all such cases are potentially erythroblastotic, we should expect the incidence of erythroblastosis to be 23.8 per cent. However, the frequency of clinically diagnosed cases has never approached this figure. The recorded incidence is about one in 200 births, or about one half of one per cent. Obviously the difference between 23.8 per cent and one half of one per cent is a pretty big discrepancy, and it is of importance to explain it.

First of all, it has been observed that of the three Rh antigens, only Rh<sup>o</sup> is of any great importance in producing symptoms. There have been a very few cases reported of effects due to immunization with Rh' or Rh'', but the number is relatively insignificant. We may confine our attention, then, to Rh<sup>o</sup>. When we compute how often a child will be expected to have Rh<sup>o</sup> when the mother lacks it, we find that the answer is 8.5 per cent. This is much closer to the observed half of one per cent, but still far enough away to demand further investigation.

Next we recall that first-born children are seldom affected. In our American population about 31 per cent of children are first-born. Eliminating these from our calculations, we would expect 6 per cent of children to have Rh<sup>o</sup>, to be born of mothers lacking Rh<sup>o</sup>, and to be second- or later-born in the family. This further closes the gap between the expected and the observed incidence of symptoms due to Rh immunization, but still leaves a discrepancy.

Looking further, we see that the cases of erythroblastosis are not

distributed randomly among the Rh— mothers, but are grouped into specific families. This suggests that the Rh° antigen may permeate the placenta only in certain Rh— mothers, or that perhaps only certain Rh— women are capable of producing potent antibodies. It may be that both these things account for the fact that not as many cases of erythroblastosis are found as can potentially occur.

Another intriguing possibility suggests itself, and the exploration of this possibility has led to suggestive results. It is conceivable that in some instances where the antigen immunizes the mother, and the antibody in turn reaches the fetal circulation, that the effects on the fetus are different from those usually recognized as classical erythroblastosis.

In various laboratories, including our own, the search has been made for such manifestations.<sup>11</sup> The results indicate that the effects of Rh immunization are unimportant in the production of early abortions, and in the etiology of hemolytic icterus, sickle cell anemia, hydatiform mole, ectopic pregnancies, eclampsia and specific toxemia. In undifferentiated mental deficiency, however, positive results were obtained.

In 1944, Yannett and Lieberman<sup>12</sup> made an examination of the blood groups and types of the children in a school for the feeble-minded, and of their mothers. They found too many Rh— mothers in the group, and too many Rh+ children of Rh— mothers. Analyzing the results it was found that of 109 feeble-minded children, 53 were distributed among the specific types of mental deficiency such as Mongolian idiocy and spastic paraplegia. The distribution of the Rh factor was normal in these children and in their mothers. In the 56 children classified as undifferentiated mental deficiency, however, an abnormal distribution of the Rh factor appeared. There were too many Rh— mothers and too many Rh+ children from these Rh— mothers.

These results appeared to us so suggestive that we have been investigating the blood of the undifferentiated feeble-minded at the Ohio Institute for the Feeble-minded, and of their mothers (Snyder, Schonfeld and Offerman,<sup>13</sup> 1945). The results to date are as follows. Of 169 mothers of feeble-minded children, 38 are Rh—, whereas only 21 or 22 would be expected. This difference is statistically highly significant. Of 171 feeble-minded children, 27 are Rh+ from Rh— mothers, whereas we should expect only 14 or 15. This deviation is also highly significant when tested statistically.

It thus appears that the immune antibodies of the mother may pro-

duce effects on the brain tissue instead of the usual symptoms of erythroblastosis. The suggestion has been made that the immediate effect of red-cell destruction is anoxia, and that this lack of oxygen, if it occurs at a time when the brain of the embryo is in a critical stage of development, may very well cause permanent mental deficiency. As a tentative estimate of the incidence of this effect I suggest a half of one per cent.

Thus the gap between the calculated incidence of effects of Rh immunization and the observed incidence has been still further closed. It is not yet completely closed, however, and the search must continue for further, as yet unknown, manifestations. In our laboratory we have recently completed an analysis of a hundred cases of dementia praecox and their mothers. The distribution of the Rh factors agrees satisfactorily with expectation in these cases.

There is some evidence that incompatibility of A and B can cause mild symptoms in cases where the fetus has one of these antigens which is lacking in the mother. Mild jaundice of group A infants from group O mothers has been reported by Polayes<sup>14</sup> (1945). In these cases the titer of anti-A antibodies was found to be 1:700 as compared with an average of less than 1:200.

Another recent and important contribution to the rapidly developing Rh picture is the discovery by Wiener that immunization may result in either of two kinds of antibodies: bivalent, resulting in typical agglutination, or univalent, resulting, in the presence of conglutinin, in "conglutination." It is Wiener's belief that the type of manifestation of erythroblastosis depends upon which of these kinds of antibodies is produced. Since the type of antibody production may well be the result of a genetic factor, further intriguing problems are posed by this discovery.

Still another field for speculation is opened by the recent suggestion of Butts<sup>15</sup> that the malarial parasite may contain an Rh-like antigen which, through immunization, produces blackwater fever as a sequella of malaria in Rh negative persons.

Through these various examples of the growth and increasing importance of medical genetics I have tried to point out its place, shoulder to shoulder with the older sciences, as an ally of public health. Someone may ask, what about a program of eugenics as a part of public health measures? My answer is that this *is* eugenics. These things I have been describing to you form the essence of modern eugenics.

In the continuing struggle for the health and well being of all mankind, medical genetics stands ready to join those sciences which have already made so much progress, in the hope and belief that its contribution may likewise prove a worthy one

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## FIBROUS DYSPLASIA OF BONE\*

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THE disorder which Doctor Lichtenstein and I<sup>1,2</sup> designate as "fibrous dysplasia of bone" has, as its central and constant feature, a characteristic kind of skeletal lesion developing in the interior of affected bones. In any particular case, one, several, or many bones may be involved, and part or much of the interior is occupied by a tissue which is basically fibrous and gritty though it may also present other features, which will be brought out later. In some cases, the skeletal aberration constitutes the entire disorder, so far as one can tell. In other cases, the disorder is expressed as an association of the skeletal aberration with the presence of one or more non-elevated light yellow or yellow-brown areas of cutaneous pigmentation. Stauffer, Arbuckle, and Aegerter<sup>3</sup> have also described a case in which, in addition to extensive skeletal changes and a large, brownish pigmented patch on the back, there were multiple congenital arteriovenous aneurysms in the left upper extremity and apparently also in the left lower

However, the vast majority of the cases of fibrous dysplasia is constituted by those showing only the dysplastic skeletal changes (in one, several, or many bones) or such skeletal changes along with some abnormal cutaneous pigmentation. The small percentage of cases remaining can be held to represent the full-blown form of the disorder. In this form, specifically, the patient presents the skeletal changes (usually together with some abnormal pigmentation) and also shows, or has shown, premature skeletal maturation and precocious puberty, sometimes along with hyperthyroidism and even some other abnormalities.

It is these full-blown cases that are commonly denoted as instances of Albright's disease,<sup>4,5</sup> though McCune and Bruch<sup>6</sup> called attention to them at the same time and then already mentioned, as did Albright, a number of cases previously reported in the literature under various titles. The case reported by McCune and Bruch represents one of the

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most carefully followed instances of the disorder, having been studied clinically by them over a period of about 6 years and then, at the time of the patient's death at the age of 12½ years, anatomically by Sternberg and Joseph<sup>7</sup> on the basis of a complete autopsy. In spite of their relatively small number, these cases bulk large in the literature, because their spectacular qualities make them attractive subjects for reporting.

We estimate that for every case of the florid type there are 20 or 30 cases of the type which we have emphasized—that is, cases in which the fibrodysplastic involvement of the skeleton is not associated even with any striking cutaneous pigmentation, apparently not with any skeletal precocity, and certainly not with sexual precocity and/or hyperthyroidism. Various observers, including Uehlinger,<sup>8</sup> have confirmed the identity of the skeletal lesions in the latter type with the skeletal lesions in the cases called cases of Albright's disease. Indeed, as stated by Falconer, Cope, and Robb-Smith,<sup>9</sup> "Albright's disease must be regarded as an association of cutaneous pigmentation and endocrine disturbances—of which the most striking is precocious puberty in girls—with a characteristic skeletal disorder [fibrous dysplasia of bone] which may occur by itself." However, though actually denoting only the dysplastic skeletal changes common to all cases, the term "fibrous dysplasia of bone" as applied to the disease complex as a whole has the advantage that it emphasizes the central and constant feature of the disease complex and can be qualified in accordance with the special features of individual cases.

We know nothing of the etiology of the condition, but the systemic character of the disease complex as a whole strongly suggests that it has its basis in some deep-rooted developmental defect, though it does not show any familial or hereditary factor. In a sense, the individual bone lesion may be conceived as a hamartoma—that is, a tumor-like malformation resulting from flaws of development and characterized by defects of tissue combination.

#### CLINICAL AND ANATOMIC ASPECTS OF THE DISORDER

No useful purpose would be served by repeating here the details on the disorder as a whole which were given in the article of 1942 by Lichtenstein and the present writer.<sup>2</sup> The reader is also referred in this connection to the excellent review article by Falconer, Cope, and Robb-Smith.<sup>9</sup> We shall limit ourselves here to orienting remarks on the clinical

and anatomic features of the disorder as a whole, and consider in their appropriate connections some features which we have not stressed before

Fibrous dysplasia of bone is by no means a rare disorder, our own experience with it now includes at least 30 cases. The disease is definitely more common in females than in males. Most of the cases come to light during childhood or adolescence, from some complaint (pain, deformity, fracture, etc.) referable to changes in some bone or bone part. The florid cases in females usually come to light quite early in childhood, on account of precocious puberty, though abnormal cutaneous pigmentation and even skeletal difficulties may have been present previously. On the other hand, in clinically mild cases in which the disease is limited to involvement of one bone or at most a few bones, the condition may remain clinically silent even until late in adult life and even then be discovered only accidentally.

*Topography and Anatomy of the Dysplastic Skeletal Lesions* As noted, in any particular case, one, several, or many bones may be affected, and, strikingly, in the cases showing multiple bone involvement, this tends to be exclusively or at least predominantly, on one side of the body. Furthermore, within a given affected tubular bone, the disease is nearly always limited to the shaft. When one bone is involved, this is often a rib, a femur or tibia, or a facial bone (particularly a jaw bone) but may be almost any bone. When a number of bones are involved, these are quite likely to be bones of one limb bud—especially a lower one. Typically, then, one finds the femur, tibia, and fibula affected, and perhaps also some bones of the foot and part of the innominate bone on the same side. On the other hand, there are cases in which, though only a limited number of bones are involved, these are exclusively trunk bones—for instance several ribs (not necessarily on one side), alone or with several vertebrae.

These cases in which a limited number of bones are affected merge without sharp delimitation into those cases in which the skeletal involvement can be said to be moderately or frankly severe. Thus one sees cases in which, while the lesions are located particularly in bones of the upper and lower limb on one side of the body, there are also at least some in limb bones on the other side, along with lesions of some skull bones, ribs, and pelvic bones, especially on the side on which the limb bones are more extensively affected. All in all, the tendency toward

restriction of involvement to the bones of one limb bud, or at least more heavy involvement of the bones on one side of the body when bones of the thorax and skull and bones of more than one limb bud are implicated represents an important clinical and roentgenographic hallmark of the disease

An affected bone or bone area may retain its original contour. Often, however, the contour is distended, at least in part, because of erosion of the cortex from within and the yielding of the newly formed cortex to internal pressure. In either case, as noted, the interior of the affected bone or bone area is found to be filled mainly by an evenly whitish or reddishly speckled rubbery and compressible tissue. Fundamentally, this is fibrous connective tissue. It may be gritty throughout from the presence everywhere in it of newly formed trabeculae of immature bone. Or, instead, it may show some smaller or larger non-gritty, highly collagenous areas in which few if any bone trabeculae are to be seen. In some lesions, islands of hyaline cartilage may also be present within the fibrous connective tissue. Furthermore, in an occasional lesion, focal degeneration of, or hemorrhage into, this tissue may have led to the formation of smaller or larger secondary cysts. In areas of organizing hemorrhage, a few scattered or clumped multinuclear giant cells may be observed. In an occasional lesion one may find some nests of foam cells within the fibrous tissue. These may be seen in connection with hemorrhage or focal degeneration of the connective tissue cells and hardly represent a noteworthy feature of the condition except in so far as they may lead to a mistaken diagnosis of lipogranulomatosis (Schuller-Christian's disease). Finally, in some areas or some lesions, so much new bone may form in the connective-tissue substratum that the latter sinks into the background and the replacement tissue has a definitely osseous character.

#### *Roentgenographic Appearance of the Dysplastic Skeletal Lesions*

The roentgenographic picture presented by an affected bone or bone area is determined in its essentials by the character of the replacement tissue in the bone interior and by the effects of this tissue on the neighboring cortical bone. Thus this picture varies from one affected bone area to another in accordance with the degree to which the bone contour has been expanded by erosion of the cortex, ridges have developed upon the inner aspect of the newly formed cortex, new bone has been formed in the connective-tissue substratum, and this tissue has under-

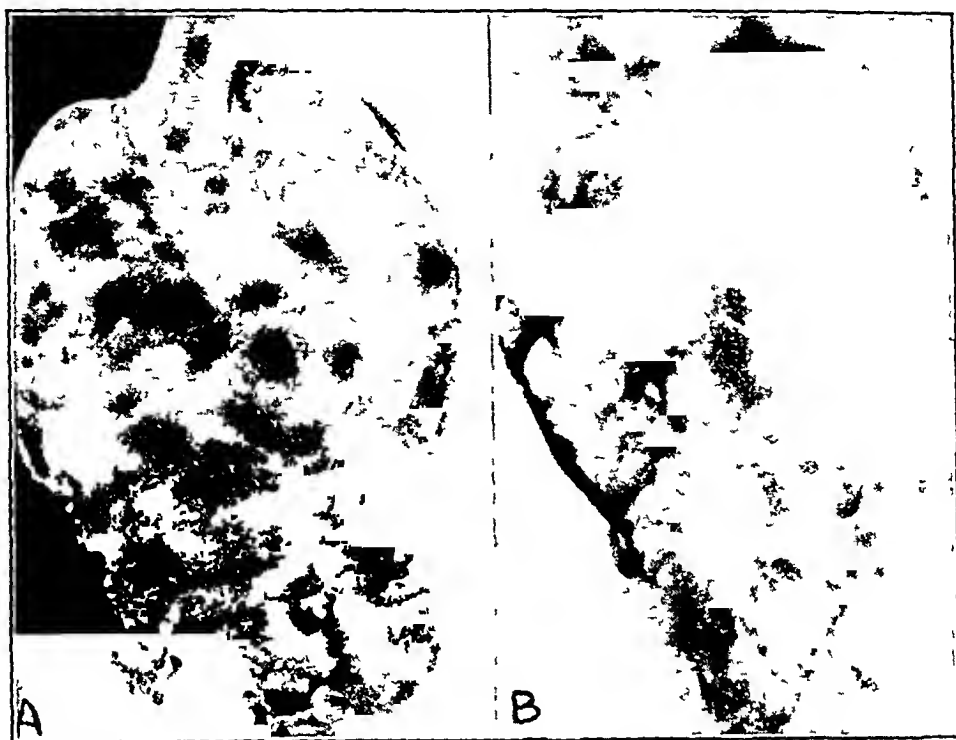


Fig 1 A Photograph of cut surface of distended anterior part of left 7th rib from a case of fibrous dysplasia in a woman of 35 in whom several other ribs and a number of vertebrae were also involved

Fig 1 B Roentgenograph of sectioned half of the rib shown in Fig 1 A Note the multiloculated shadow Actually, the interior of the rib is entirely filled with fibro-osseous tissue The loculated shadow results from ridging on the interior of the cortical shell

### gone cystification

In lesions or parts of lesions in which the replacement tissue in the interior of the bone is not highly osseous or is cystic in part, it will tend to cast a rather radiolucent shadow. In lesions or parts of lesions in which the replacement tissue has undergone extensive ossification, it will tend to cast a shadow resembling ground glass or spirals of smoke. If the replacement tissue has eroded the original cortical bone and distended the newly formed cortex, and if the latter has bony ridges on its inner surface, the affected area may present a "multilocular" appearance, although, as tissue examination has repeatedly shown, the area in question may actually be solidly filled by the basic fibro-osseous tissue.

*Abnormal Cutaneous Pigmentation* Of the other manifestations seen

in cases presenting the fibrodysplastic skeletal lesions, the most common is abnormal cutaneous pigmentation. A pigmented skin area is not elevated, has the same texture as the rest of the skin, and is yellowish or yellowish brown. The discoloration reflects (as others also have found) the presence of an abnormal amount of melanin pigment, particularly in the basal cells of the epidermis, though some of the cells of the granulosa layer may also show pigment granules and an occasional pigment-bearing cell may likewise be seen in the corium. Otherwise, a pigmented skin area does not differ histologically, either, from the unaffected adjacent skin. We do not know, as yet, the explanation for the pigmentation.

An abnormally pigmented area may appear as a small uniform patch, a patch of clustered freckles, a large blotch, or a very extensive field. There can be no doubt that when the pigmentation is not extensive and the pigmented area or areas are light yellow, it may be overlooked, as indeed it was in one of our earliest cases. In a case of fibrous dysplasia which we saw recently, in which the skeletal involvement appeared to be limited to a single bone, the patient presented a number of abnormally pigmented skin areas. However, abnormal cutaneous pigmentation is certainly not seen in all the cases, and is thus not a necessary accompaniment of the fibrodysplastic skeletal changes. Indeed, the writer has seen some patients in whom the skeletal involvement was fairly severe but in whom careful search, including examination of the scalp and buttocks, failed to reveal a single patch or blotch. In such cases, one may, it is true, find some scattered individual freckles on the upper part of the back, or an occasional pigmented or vascular nevus. However, everyone recognizes the commonness of these in the general population, even at the younger age levels, and one cannot attach to them the same significance that belongs to a patch or blotch or to an area of pigmentation constituted by freckles gathered in a cluster.

Sometimes, the site of the abnormal pigmentation corresponds to that of severe skeletal involvement. However, the cutaneous pigmentation may be in a region where the bones are not affected. Thus, in one of our cases, in which the only focus of fibrous dysplasia was in the upper portion of the shaft of a femur, a patch of cutaneous pigmentation several inches in diameter was present on the dorsum of the foot on that side. In another case, in which the fibrodysplastic changes were in bones of the right lower limb bud, a single patch of cutaneous pig-

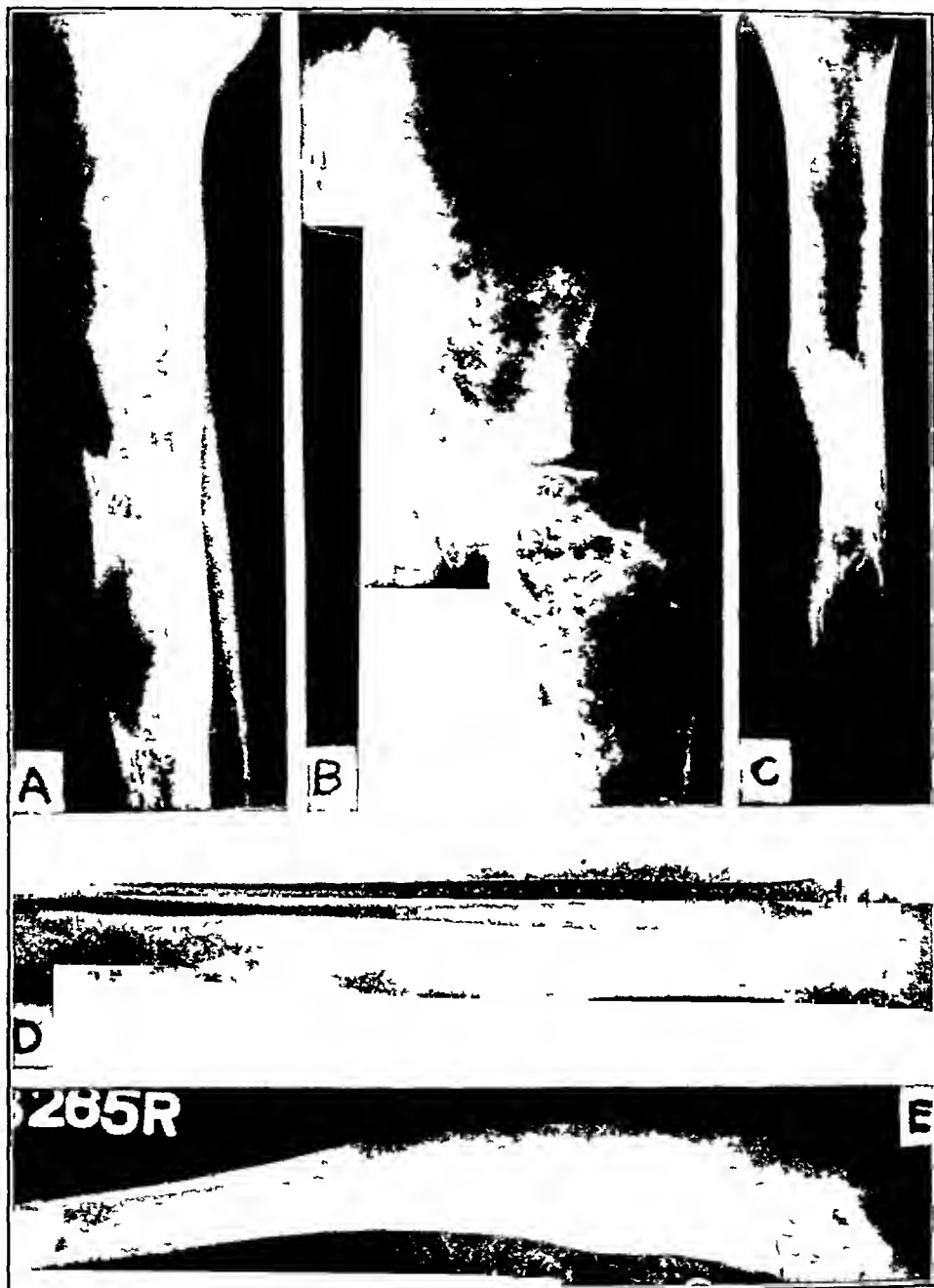


Fig 2 A, B, and C Roentgenographs of the left tibia, innominate bone, femur, and humerus, in a case of fibrous dysplasia in a girl of 24 in whom a number of other bones were also involved. Compare the multiloculated shadow cast by these bones with the appearance of the bones shown in figures 2 D and 2 E, which are from another case.

Fig 2 D and E Roentgenographs of the right tibia and femur in a case of fibrous dysplasia in a girl of 9 in whom the right innominate bone and some bones of the right foot were also involved. In this case, the affected bone areas cast a "ground-glass" shadow. This appearance is due, as tissue examination showed, to the presence of considerable new bone in the fundamentally fibrous replacement tissue.

mentation was found on the skin of the middle of the left leg

*Skeletal Precocity* In some cases, both skeletal growth and skeletal maturation (that is, the ossification and fusion of epiphyses) are accelerated. These two effects work at cross purposes. Thus, for a time during childhood, the patient may be excessively tall for his or her age and show a skeletal age several years in advance of the chronological age. However, because there is premature epiphysial fusion, the ultimate height of the patient is usually below the average.

Knowledge of the occurrence of the skeletal precocity has been derived mainly from cases in which the fibrodysplastic skeletal lesions were pronounced and associated with sexual precocity. However, Falconer, Cope, and Robb-Smith state that skeletal precocity may be present even in the absence of sexual precocity. Whether it occurs in the milder cases—for instance, those in which the bones of one limb bud alone are involved—is difficult to say, for often these cases do not come to light until near the end of the growth period. In one case of this type seen recently, in which the patient was a girl of 9, and in which I studied the x-ray films of the entire skeleton, I could not find evidences of skeletal precocity on the basis of the usual standards for measuring the same. This was true also in another recent case—that of a girl just 19 years of age in whom the fibrous dysplasia was apparently limited to a tibia but who also showed several patches of cutaneous pigmentation. In this patient, the skeletal age as evaluated from the epiphysis for the crest of the ilium and that for the ischium corresponded exactly to the chronological age. The basis for the skeletal precocity in those cases in which it is found is apparently some endocrine imbalance.

*Sexual Precocity* We come now to the question of the sexual precocity found in a small proportion of cases of fibrous dysplasia—especially those in which the skeletal lesions are pronounced and extensive. This precocity was at first thought to occur exclusively among the female patients, but several instances of its occurrence in male patients also have now been reported.<sup>9</sup> In the female, it is manifested in catamenia at an abnormally early age (as early even as the first year of life), enlargement of the external genitals, and the appearance of secondary sex characteristics, notably the development of large breasts showing prominent areolae, and the growth of pubic and axillary hair. The onset of precocious menstruation often coincides, more or less, with the genital hypertrophy and the premature appearance of the



secondary sex characteristics In the male, of course, the sexual precocity follows the male pattern All the studies which have been undertaken in regard to the gonadotropic, follicle-stimulating, or estrogenic hormone content of the urine of these subjects have failed to yield any abnormal findings Nor do the sex glands themselves show anything abnormal Possibly there is, in these cases, an abnormality or lesion in the hypothalamus, conditioned by the fibrodysplastic changes in the skull However, there is no basis for holding, as some<sup>10</sup> have held, that the fibrodysplastic skeletal lesions have their basis in the endocrine imbalance which necessarily underlies the sexual precocity Finally, it is of interest in connection with the latter that there are a few recorded instances in which female patients who showed sexual precocity have later gone successfully through pregnancies and given birth to children who showed no signs of the disease

*Other Associated Phenomena Occasionally Observed* In an occasional instance of fibrous dysplasia, such diverse phenomena as hyperthyroidism, congenital arteriovenous aneurysm, rudimentary kidney, and visual disturbances from pressure atrophy of the optic nerve have also been observed

#### COURSE OF THE DISEASE IN THE SKELETON

*Tendency toward Stabilization* Our experience favors the belief that the period of active progression of the skeletal involvement tends to end when adult life is reached, in the sense that bones which were not involved by this time do not begin to become so now Thus, even when fibrous dysplasia of bone is first uncovered in adult life, the skeletal lesions apparently date back to childhood It is true that in a case showing extensive skeletal involvement already in childhood, one or more of the severely affected bones may show progressive deformity in adult life However, this is due to weakening of the bone, and is not inconsistent with the appearance of increasing ossification of the fibrodysplastic tissue as another aspect of the process of stabilization In fact, in some cases (particularly in the skull though also in some long bones) sclerotization of the fibrodysplastic tissue may become very pronounced Indeed, it may progress to such a degree that the roentgenographic appearance of the affected bones may even suggest Paget's disease Should such sclerotized tissue be subjected to anatomic study, it may actually be misinterpreted as representing Paget's disease, by one

not thoroughly familiar with the latter or with the nuances of the histopathology of fibrous dysplasia. At any rate, what we have said so far in general about stabilization of the bone lesions does not preclude the occurrence, in certain cases, even during adult life, of tremendous increase in size of the lesion in one or another of the affected bones, as will now be brought out.

*Rapid Enlargement of the Lesion in One or Another Bone without Evidence of Malignant Transformation* The fact that lesions which may have been stabilized for years can take on some growth activity has been familiar to us for some time. Thus a patient may come in even during middle life because of complaints of only recent origin, due to a spurt of growth (perhaps quite slight) in a lesion which has clearly been present for decades. Relative rapid exuberant growth of one or more fibrodysplastic lesions is infrequent, but was illustrated in one of our cases. The patient was first seen at our hospital in 1940, when she was 35 years of age. She stated that when she was 9 she had a flow of blood from the vaginal region which persisted for 3 or 4 days, that she was given some medication by mouth for this, and that she had no further vaginal bleeding until the age of 16, when menstruation set in. She presented no non-elevated pigment patches or blotches, though she did show, on the skin, a number of small, scattered, elevated pigmented nevi and some vascular nevi. Her first difficulty relating to the skeleton appeared when she was 27 years old, in the form of a large lump on the left side of her chest and specifically in the left 7th rib anteriorly. This lesion was enlarging and had not been controlled by radiation, and she was admitted for its surgical removal. Roentgenographic examination now showed, however, that the posterior part of the left 7th rib was also affected, and that the 7th and 8th ribs on the right side were extensively involved, as were several dorsal vertebrae. The anteriorly affected part of the left 7th rib was removed by Doctor Leo Mayer, and beyond the costal cartilage the rib was found expanded to the size of a large pear by fibrodysplastic tissue of characteristic histology.

The patient was then well for 2 years, when, because of a spurt of growth occurring in the bodies of some of the affected vertebrae, she developed signs of pressure upon the spinal cord, at the dorsal level. At the surgical intervention, the compressing tissue which was growing out of the bodies of the dorsal vertebrae was removed, and the patient



Fig 3 A and B Note the huge tumor mass on the right side of the chest. It was from this patient, now 40, that the left 7th rib shown in Fig 1 had been removed 5 years earlier. At that time, the right 7th and 8th ribs were already known to be affected, but the tumor mass now present on the chest was not there then. It developed rapidly, in the course of a few months, as a result of progression of the previously existing lesion in the right 8th rib, as shown in Fig 3 B.

Fig 3 C Photograph of sectioned tumorously expanded right 8th rib, which produced the appearance shown in Fig 3 A. Note the cysts and the solid tissue below them. The ball-like mass to the right was composed of collagenous connective tissue with little new bone in it.

made a substantial recovery. In 1944, there was a recurrence of the cord symptoms, she was re-operated upon, and additional fibro-osseous tissue was again removed extra-durally from the dorsal region. The laminectomies were done at Mt Sinai Hospital by Doctor Ira Cohen, and Doctor Paul Klemperer kindly gave me the opportunity of examining the slides from the material removed at both these interventions—tissue which showed the pathology typical of fibrous dysplasia. Also in 1944, but some months after the second laminectomy, the patient began to develop, on the right side of the chest a tumor mass which rapidly attained huge proportions. This mass resulted from a tremendous enlargement of the lesion which earlier films had shown to be present in the right 8th rib.

This rib, together with the fibrodysplastic 7th rib and the uninvolved 9th rib, were removed by Doctor Leo Mayer in one mass, which was approximately of the size of a standard football. When it was sectioned in its long axis, the exposed cut surface showed that fully half of the mass was represented by a huge multilocular cystic area in which some of the cysts were filled with clotted blood and others with yellow-green fluid. The rest of the mass was made up of one large oblong area, composed of quite gritty fibrous tissue, and one ball-like area of highly collagenous tissue with little if any grit in it. Though clinically we seemed to be dealing now with a sarcoma which had developed in a fibrodysplastic rib, the gross appearance of the lesion already made it necessary to reject this diagnosis. Furthermore, histologic examination of great numbers of tissue blocks from every part of the lesion also failed to show any evidences of malignancy. It is in harmony with these findings that during the 1½ years which have elapsed since removal of this great mass, the patient has felt in better health than she had had for many years before, and has gained in weight and strength.

*Sarcoma Appearing in a Case of Fibrous Dysplasia* Until recently, we had neither seen nor read of any cases of fibrous dysplasia in which a sarcoma appeared. In 1945, Coley and Stewart<sup>11</sup> called attention to 2 such cases. In their first case—that of a woman 42 years of age when first seen—there was a massive osteolytic tumor of the left scapula, along with fibrous dysplasia in the skull, some ribs (particularly on the left), the left humerus, ilium, and femur, and the right pelvic bone and femur, associated with extensive abnormal cutaneous pigmentation. The tumor of the left scapula proved, on punch biopsy, to be a non-bone-forming

sarcoma, while examination of tissue from one of the ribs established the diagnosis of fibrous dysplasia in regard to the rest of the skeletal lesions. In their second case—that of a man 34 years of age when first seen—there was a massive tumor involving the left hip region, while the left pubic bone, femur, and tibia showed roentgenographic alterations consistent with a diagnosis of fibrous dysplasia. The tumor in the hip region proved, on punch biopsy, also to be a non-bone-forming sarcoma, while a biopsy specimen from the tibia showed evidences of fibrous dysplasia. The patients in the 2 cases survived for 11 and 4 years, respectively, and died presumably from metastases, but in both cases the course run by the primary malignant tumor was unusual in that small doses of radiotherapy apparently held it in check for a long time.

Since publication of the paper by Coley and Stewart, the writer has studied material from a case of fibrous dysplasia involving bones of the right lower limb, in which a sarcoma developed in the fibrodysplastically involved tibia. The limb was amputated through the middle of the femur, and I was able to study, both grossly and microscopically, a longitudinal half of the removed femur, tibia, and fibula, through the courtesy of my colleague Doctor (now Major) Charles Sutro. Doctor Sutro plans to report this case in detail. Here a very brief sketch will suffice. The patient was a man of 25, whose first difficulty relating to his skeleton was of only a few months' standing and consisted of some pain in the right leg and the appearance of a slowly enlarging swelling in the middle of the tibia. Roentgenographic examination revealed the presence of fibrous dysplasia, of which, as noted, the patient was entirely unaware, involving the right femur, tibia, and fibula, and of a bone-forming sarcoma more or less in the middle of the shaft of the tibia. Both grossly and histologically, the sarcoma proved to be an osteogenic sarcoma. Below the sarcomatous area, the marrow cavity of the tibia contained non-sarcomatous fibro-osseous tissue such as one sees in sclerotized fibrous dysplasia lesions. Similar tissue was observed in the marrow cavity of the femur specimen and fibula specimen. However, even in the tibia, in the region of junction between the sarcoma and the fibrodysplastic tissue, the latter showed nothing which could be interpreted as representing presarcomatous transformation of the fibrodysplastic tissue. Thus, all that one could safely say about this case is that an indubitable osteogenic sarcoma developed in the tibia, which latter still showed evidences of fibrous dysplasia.



Fig 4 A, B and C Photographs of part of femur, tibia, and fibula, respectively, from the right lower limb of a man of 25. There is an osteogenic sarcoma (Fig 4 B) in the tibia, while the femur (Fig 4 A) and the fibula (Fig 4 C) show tissue characteristic of fibrous dysplasia in their interiors. There was evidence of fibrous dysplasia also in the lower half of the tibia which was the site of the osteogenic sarcoma.

#### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of fibrous dysplasia can usually be made on clinical grounds, including the roentgenographic appearance of the affected bone or bones. This is particularly true when a number of bones are involved. The tendency of the involvement to be restricted to the

bones of one limb bud or at least to be predominantly on one side of the body is another valuable criterion. When only one bone or part of one bone is involved, definitive diagnosis has to rest on tissue examination, since in such cases the roentgenographic differentiation between fibrous dysplasia and solitary bone cyst, enchondroma, or even a fibroma of bone cannot always be made. Some (for instance Dockerty and his associates<sup>12</sup>) imply that one cannot make a diagnosis of fibrous dysplasia on the basis of a bone biopsy examination alone, and in particular that one cannot differentiate on this basis between the histologic picture of fibrous dysplasia and that of hyperparathyroidism. The fact is, however, that the essential pathologic picture presented by an adequate bone biopsy specimen is different in a case of fibrous dysplasia from what it is in hyperparathyroidism. Indeed, if the examiner has a firm grasp on the pathology of the bone lesion in fibrous dysplasia, he will easily be able to distinguish it not only from the bone lesions of hyperparathyroidism, but from all other bone conditions, on the basis of histologic examination.

In cases of fibrous dysplasia, the only aberration which one may find in the blood by clinical biochemical analysis is an elevation of the serum alkaline phosphatase activity value. Though in some cases, in spite of the fact that many bones are involved, this value is hardly above normal, in other cases we have found it as high as 17 or even 20 Bodansky units. The fact that the serum calcium value is never elevated in fibrous dysplasia immediately differentiates it on this basis alone from hyperparathyroidism. In cases of fibrous dysplasia in which mineral balance studies (calcium and phosphorus) have been done, these have always yielded values within the normal range, which is again not what is encountered in hyperparathyroidism.

In the writer's experience, the only condition which can sometimes raise the problem of differential diagnosis on a clinical basis is skeletal enchondromatosis of the Ollier type—that is, enchondromatosis limited to some bones of one limb bud or involving predominantly the bones on one side of the body. However, in these cases, if hand or foot bones are involved, the punched-out rarefactions in the shafts of the phalanges and metacarpal bones and the bulging of the contours of some of them, as seen roentgenographically, are almost sufficient in themselves to show that the condition is enchondromatosis. Anatomically, of course, in the latter, the abnormal tissue occupying the interior of the affected bones

is basically hyaline cartilage, so that there is no possibility of confusion with the abnormal tissue in the interior of bones affected with fibrous dysplasia

Finally, in respect to differential diagnosis, we come to the contention of some that fibrous dysplasia of bone is not a disease entity at all, but a variant of some other disorder. Thus Snapper<sup>13</sup> maintains that it is to be linked with Hand-Schuller-Christian's disease (lipoid granulomatosis) as an atypical clinical expression of that disorder. However, the clinical, roentgenographic, topographic anatomic, and histologic anatomic differences between the two disorders are so great that there should be no confusion between them. The distinctions have already been emphasized by the present writer<sup>14</sup> in another connection. In that connection, he devotes attention mainly, however, to the lack of validity of Thannhauser's contention<sup>15</sup> that fibrous dysplasia of bone (or, as he prefers to call it, osteitis fibrosa cystica localisata et disseminata) is not an independent entity, but is to be related by its clinical and histological features to neurofibromatosis of Recklinghausen. Here it will suffice to point out again that the skeletal lesions which are the central feature of fibrous dysplasia of bone find no counterpart in the skeletal aberrations occasionally found with neurofibromatosis.

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## SURGICAL PRINCIPLES IN WOUND MANAGEMENT\*

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THE wounds of warfare vary but little from those of civil life except in two respects first, they occur in epidemic form, and, second, there is a special group caused by high velocity missiles Such missiles produce an explosive effect within the tissues, with the lines of force extending in an oblique, radiating fashion Such a wound consists of three zones (1) the wound track itself with its debris, (2) a zone of devitalized tissues, and (3) an area of contused cells and hemorrhagic exudate

We often think we have discovered something new, only to find that we are merely reaffirming old principles Man has forever sought some panacea to place on or in a wound to insure its healing, and all sorts of applications and concoctions have been used We have run the whole gamut of boiling oil and cracked ice, of polypharmaceutical lotions, ointments, and complicated chemicals, of light rays and gases, of vegetables and minerals, and of animal life and material both quick and dead Eventually all these drop into their proper places, and fundamental principles reassert themselves

### THE PAST

In the year 1214 the city of Bologna made contract with a certain Ugo of Lucca to perform the surgery for six months of each year, and in case of war to treat the soldiers free<sup>1</sup> Ugo was already past middle life and it is not definitely known where he obtained his medical education He had four children, three of whom practised medicine in Bologna, and the oldest of these was Teodorico, who learned his medicine from his father and was destined to become even more famous Both Ugo and Teodorico made their greatest contribution to modern

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surgery in the refutation of the belief that pus in a wound is good Teodorico (Theodoric, A D 1205-1296) urged simple cleanliness, the avoidance of drains, and recommended simple dressings of wine compresses and plain gauze He did not use the cautery and paid much attention to the general nutrition of his patients

"For it is not necessary," he says in his *Surgery* written in 1266, "as Roger and Roland have written, as many of their disciples teach, and as all modern surgeons profess, that pus should be generated in wounds No error can be greater than this Such a practise is indeed to hinder nature, to prolong the disease, and to prevent the conglutination and consolidation of the wound Pus destroys and increases the size of a wound"<sup>2</sup>

Medicine and surgery at this time sorely needed reform from the Galenical principles of salves and tents and the polypharmacy then so rife, and this change was taught by Theodoric, "who produced beautiful scars without the use of any ointment"<sup>2</sup>

One of his contemporaries was William of Saliceto who held similar views against the theory of "pus laudabile" Less is known of him but his most famous pupil, Lanfranc of Milan, pays him high tribute Lanfranc, writing in Paris in 1296, states that the wound should be clean and dry and bleeding should be controlled by ligature if necessary, drains, or "tents," should not be used, and one must be careful to include all layers in the suture so as not to leave a dead space He advised that a powder, one of the ingredients of which was lime, be employed as a dressing so as to keep the wound dry<sup>3</sup>

The most famous pupil of Theodoric was Henri de Mondeville, the greatest of the early French surgeons De Mondeville studied with Theodoric and carried that master's philosophy of the surgery of wounds back to France with him It is not clear whether or not he ever worked with Lanfranc, then settled in Paris, but he refers to him with considerable respect As one of the royal surgeons under Philip le Bel he was also associated with Jean Pitard, who apparently believed in the same surgical principles De Mondeville appealed for cleanliness, hemostasis, and for simple careful dressings which should not be disturbed for several days Should heat and pain develop, then the wound must be reopened and washed out again or poultices applied Needles should be triangular, sharp and clean, "or they will infect the wound,"<sup>4</sup> and there should be grooves by the sides of the eye so that the thread

would not cause further damage as the flesh was pierced. Every cause of the formation of pus must be avoided. His comments were somewhat caustic as he said that "many more surgeons know how to cause suppuration than to heal a wound,"—<sup>1</sup> a statement that held true for six hundred years.

But this courageous little group marched with a flickering light through the darkness of the period. They flowered in the earliest dawn of the Renaissance, for over a century from 1214-1325, but finally, with the death of de Mondeville, the light went out, and with Guy de Chauliac there was a return to the Galenical theories of salves, tents, and laudable pus. At a time when it was dangerous to express one's views and against the strong opposition of the medical world they had the courage of their convictions and it was not until almost five hundred and fifty years later that Lister finally proved to the world that these truly remarkable men—Ugo da Lucca, Theodoric, William of Saliceto, Lanfranc, and de Mondeville, were right.

As we pass through the Renaissance we come upon a new kind of wound, that caused by gunshot, first mentioned by John of Vigo in 1514 and later in the same century studied more carefully by Paré. He was the first to attempt to trace the course of bullets by placing the patient in the position he was in when hit, and also recognized that the effects of a gunshot wound were chiefly due to contusion and laceration rather than to burning and actual poisoning of the tissues. He turned away from the use of the cautery and boiling oil in these wounds and improved the ligature, thereby reducing secondary hemorrhage, and so made major amputations possible with comparative safety.<sup>2</sup>

Notwithstanding the progress in anatomy, physiology, pathology and physics and the discovery of the microscope and "animalculæ" by van Leeuwenhoek during the seventeenth century, surgery remained almost completely static. Still another hundred years later we find John Hunter, in his extensive treatise on wounds, admitting that wounds with external communication commonly inflame and suppurate and further if ligatures are used, wounds *will* suppurate. In considering the possibility of primary healing he says that "this method is probably limited to some certain distance of time after the wound has been received perhaps the sooner it is done, the better."<sup>3</sup> Plaster he considered to be superior to sutures as there was less danger of suppuration. Tension, he thought, was the natural consequence of wounds and

no better results were obtained by opening gunshot wounds, though each wound should be judged of itself

The observations of Semmelweis and Pasteur prepared the way for the final vindication of the tenets of Theodoric and de Mondeville by Lister in his original work with phenol and phenol paste on compound fractures In his report in 1867 he says

"All the local inflammatory mischief and general febrile disturbance which follow severe injuries are due to the irritating and poisonous influence of decomposing blood or sloughs" The initial antiseptic dressing was to protect the wound from infection from without but after the first dressing the object in contact with the tissues should be as bland and neutral as possible<sup>6</sup>

"Injured tissues do not need to be 'stimulated' or treated with any mysterious 'specific', all that they need is to be let alone"<sup>7</sup> He further recognized the danger of tension by pointing out that it is sometimes well to avoid stitching and the tension that may be associated with it, and a clean blood clot which contracts makes an excellent dressing<sup>8</sup>

Building upon the firm foundations of Lister a young American surgeon, W S Halsted, in 1891 enunciated the fundamental surgical principles in the healing of wounds At this time Lister was then 64 and his great work had already been accomplished, Halsted was but 39 and was on the threshold of his brilliant career He saw fully what the work of Lister had made possible and realized that the field of surgery should and could be extended still further by more careful handling of the tissues and attention to detail Infection was now understood, true, but it was by no means well controlled In his initial article on the treatment of wounds Halsted says, referring to Lister

"He has taught us what can be done under the cover of antiseptics One may maltreat the tissues to any extent—mutilate the wound during the operation in every possible way, cut off by ligatures the circulation in large masses of tissue, produce extensive areas of superficial necrosis by irrigation with antiseptic solutions, stuff the wound with gauze and drainage tubes, tear out the stuffing and with it the granulations which have grown into it, restuff, etc—and still the wound may heal without suppuration, without septic inflammation, and in a way which is, perhaps, altogether satisfactory to the surgeon"<sup>9</sup>

By this statement Halsted well judged the temper of the average surgeon as he rushed into the new fields of surgery that had been

opened by Lister. Both the dangers and future possibilities were clearly understood by Halsted in his approach to and establishment of our present aseptic surgery. He turned away from catgut to the silk ligature because silk was more uniform and could be completely sterilized. Silk being non-absorbable, unless strict asepsis and great attention to detail were practised, clean healing would not result and foreign body sinuses would persist. This could be avoided, however, by a proper technique. The essential principles in the treatment of wounds then, are (1) the employment of fine sutures, (2) delicate handling of the tissues, (3) partial obliteration of dead spaces, (4) not irrigating the wounds with disinfectants or using mass ligatures or drains, and (5) applying dressings with gentle even pressure.<sup>9</sup> For many years these measures were considered by many as meticulous and unnecessary, but as the standards and scope of surgery have increased these precepts have gradually become generally accepted.

In military surgery a similar evolution in the treatment of wounds was developing as the important role of foreign bodies and dead tissue in the causation of infection became increasingly apparent. This is admirably described in the British official history of the Great War.

"The treatment of wounds by free excision at the casualty clearing stations was generally adopted as an alternative to the use of free incisions for drainage, and after the year 1915 it became a common practice during quiet periods. It could not, however, be employed at that time during a battle because of the small size of the clearing stations and the scarcity of their surgical personnel, and it was not until the first battle of the Somme in 1916 that it began to be adopted at the front on a large scale. From that time on it was the regular practise, and was proved to be the most efficacious means for the prevention and arrest of gas gangrene. The earlier this treatment was carried out and the more thorough the removal of all torn muscle and foreign bodies, the more satisfactory were the results, and during the heavy fighting of the year 1917 the large majority of all the severe wounds were treated in the casualty clearing stations by this method. Only when the numbers of wounded became too great were such patients sent to the base before operation. It was found to be most important not to excise any skin, although free incision to get at the deeper parts were commonly required.

*"Suture of Wounds*—The wounds treated by suture in the early

days of the war did badly, and as a result the closure of wounds fell into complete disuse for the next year or two. In 1917 suture was again tried, but then only under good aseptic conditions and after the excision of damaged tissues and the removal of all foreign bodies, and it was soon found that under these conditions very good results could be obtained."<sup>10</sup>

The greatest surgical advance that emerged from the First World War was the debridement of wounds. This principle was promptly adopted by us and in our own official history Pool says

"The ideal treatment of war wounds, as based on experience gained in the World War, consists in complete excision of all devitalized tissue, followed by the application of immediate or secondary suture, according to conditions existing in a given case."<sup>11</sup>

### THE PRESENT

As surgeons we must treat wounds caused by trauma and we must ourselves make wounds, for the performance of elective surgery and for the treatment of infection. Hence we must be interested in the repair of tissues and the healing of wounds subsequent to trauma and of our own fashioning. Tissue repair is a complex biological process, but one that we can favor or hinder according to our own actions. The ideal and least complicated wound is the non-penetrating variety involving only skin and subcutaneous tissues. Certain tissues have enormous powers of regeneration,—the corneal epithelium or liver parenchyma, some, such as cartilage and striated muscle, regenerate very slowly and repair occurs almost entirely by fibrous scar, and in some repair takes place in a dual manner, as in smooth muscle.<sup>12</sup> This inherent ability of regeneration by the tissues themselves varies considerably with age, in the lung, for example, there is probably true regeneration and hyperplasia in youth, whereas in adult life there is none.

Normally the healing of a wound is brought about by the movement and proliferation of living cells and by contraction.<sup>13</sup> When healing is complete this growth of new cells stops. Healing itself may be by apposition, as in primary union, or by granulations and scab formation. Initially there is always a certain amount of traumatic inflammation varying with the extent of tissue trauma, contamination, sloughs and foreign bodies that may be present. This exudate consists of blood

the wound secretion or plasma which is rich in fibrinogen at first, and surrounding edema. In the fresh cleanly incised superficial wound, opened and closed under aseptic and atraumatic technique, this exudate is minimal and as the edges are apposed, this secretion of plasma—the “wound balm” of Paré—agglutinates them and forms a thin cement substance, which maintains healing until the tissue repair itself takes over. With such a wound this latent period is short and has a fairly uniform time of four to six days.<sup>14</sup> This quiescent phase is an initial period of healing common in all tissues. It was noted by Carrel first in 1910 and further elaborated in 1921,<sup>15 16</sup> and depends upon both local and general factors. The local factors are (1) the amount of killed or damaged tissues in the wound surfaces and in the walls or immediately surrounding zone of the wound, (2) the vascularity of the tissues involved, (3) the integrity of the blood flow to the damaged tissue, (4) the exudate in the wound and adjacent tissues, (5) the number and character of the infectious organisms present, and, (6) the number and character of the foreign bodies to be extruded or encapsulated.<sup>17</sup>

The general or systemic factors that influence wound healing are: (1) the age of the tissues, already mentioned, (2) normal hydration, dehydration, over-hydration, (3) the general nutritional state, (4) avitaminosis, (5) the state of the circulation and the blood picture.<sup>17</sup>

During this earliest phase of repair the wound is being cleaned up by tissue destruction through autolysis from enzymes liberated by the cells themselves, by heterolysis from enzymes liberated by the leucocytes in the necrotic zones, and through the action of macrophages in removing cellular debris and in surrounding foreign bodies.<sup>18</sup> This latent, or destructive, phase is the most dangerous period in wound repair. It is prolonged by the presence of infection, debris, foreign bodies, sloughs, devitalized tissue and impaired circulation, all of which may be directly influenced by the surgical treatment of the wound. From the systemic standpoint this phase is prolonged by any of the factors already noted. True, the surgeon is powerless to influence the age of the tissues but by assuring a normal state of hydration, a well balanced high protein diet with sufficient vitamins, particularly C and B, and a normal blood picture, he can go far in compensating for the old age of the tissues. Furthermore, wounds do not heal well in the presence of severe anemia or a damaged circulation.



The second important stage in wound healing is the phase of fibroplasia, at which time active repair commences with abundant proliferation of fibroblasts. In the fresh clean wound this continues from about the fourth to the fourteenth day and it is during this time that the tensile strength of the wound is developed. The curve rises rapidly at first, reaching its maximum in ten to fourteen days.<sup>12</sup> From the practical standpoint this is the important criterion of an healed wound.

The constructive period, or phase of fibroplasia, begins very early and overlaps the destructive phase. What the actual stimuli are to wound repair is not well understood. It is thought by some that the diminished oxygen tension in the cells of the ischemic zone stimulates cell division. There may be some substance liberated in the process of cell destruction and numerous specific substances have been listed: embryonic or leukocytic extract, hormones, temperature, pressure, peptones, the sulphhydryl radical, glutathione, hemoglobin, solar ultraviolet rays and others. Within the first few hours there is a beginning migration of cells to the site of trauma with gathering and budding of the endothelial cells of the nearby vessels, the presence of leukocytes, histiocytes, macrophages and fibroblasts, and the ameboid movement and mitosis of the epithelial cells. By the second day in primary healing rapid proliferation of these cells is evident, in secondary healing, filling with granulation tissue commences in six to eight days. While destruction is still in progress, however, there is but little fibroplasia and connective tissue fibrils do not appear.

Loeb (cited by Whipple) emphasizes "the importance of two processes in this stage of the lag period connected with the ameboid movement and proliferation of the invading fibroblasts. The first is the phenomenon of stereotropic response of growing cells to surfaces. Fibroblasts in contact with fibrin strands or fibrils have a strong tendency to elongate and grow along the fibrils, just as epithelial cells show ameboid movement along plane surfaces of granulation tissue or beneath the scab. The second reaction is a centrifugal force which directs the cells away from their own tissue and into the plasma mass in the wound space. This induces various kinds of cells, including fibroblasts, to move into the clot in a fan-like manner to take part in the organization of the clot. Similarly, endothelial buds show a centrifugal growth into the organizing fibrin with a spread of the vascular bed and thus enter into the formation of granulation tissue."<sup>17,19</sup>

The third and final phase in the cycle of wound healing is that of maturation. It is in this later stage that the cells mature, the wound solidifies and contraction occurs<sup>14</sup>

If one studies histologic sections made at frequent intervals from a series of identical clean wounds, these changes are readily seen and may be followed through to the gradual elongation of the fibroblasts, the appearance of connective tissue fibrils, the disappearance of the cellular reaction and vascular granulation tissue, and the final appearance of collagen and the contraction that accompanies scar formation.

Other changes that occur in the course of healing are (1) at first there is an increase in the fluid content with increase in the electrolytes, (2) there is a demonstrable, though slight, difference in electric potential in the wound, (3) due to local stasis there is local anoxia and increased CO<sub>2</sub>, resulting in a faintly acid reaction initially, and (4) there is an early decrease in the tissue metabolism, which rises, however, with the advent of granulation tissue, blood and cells, and then slowly returns to normal as the wound heals<sup>15</sup>

From the practical surgical standpoint, if one will but visualize and think of what is taking place in a wound, particularly in the destructive phase and lag period, the need for very careful surgery at once becomes apparent. Also, one will understand the different problems of delayed primary suture between the fourth and seventh days, between the tenth and fourteenth days, and the late secondary suture of old wounds, whether formerly grossly infected or not.

In order to provide the optimum wound the following factors are of prime importance: (1) Dissection with a sharp knife (2) Complete hemostasis (3) The maintenance of as sterile a field as possible (4) Protection of the wound edges with towels, and exposed surfaces with moist abdominal pads (5) The use of as fine ligature material as possible, with not more than twice the tensile strength of the tissue in which the suture or ligature is placed (6) Minimum trauma with maximum maintenance of the blood supply and nutrition of the tissues<sup>20</sup>

These criteria of Whipple may be elaborated by adding

1. Protection of the blood supply, which consists of (a) assurance that the main supply to the part involved is intact or as adequate as possible, (b) the avoidance of tension in the wound and of strangulation of the tissues by too tight sutures. These are perhaps the two most common errors of the surgeon. Strangulation may be caused by

tension as in intestinal distension following anastomosis, this may be prevented by nasogastric drainage and the use of the Miller-Abbott tube

2 Reduction to a minimum of the foreign material left in wounds  
It is not always remembered that ligatures, drains and packs, although required by the objectives of surgery and proper hemostasis, are actually foreign bodies

3 The avoidance of mass ligatures and the devitalized tissue they cause

4 The obliteration of dead spaces

5 The application of dressings with even pressure Such a dressing helps in maintaining hemostasis, protects the plasma coagulum, and obliterates dead space

6 Rest of the part, by splints if necessary, even for soft part wounds

7 The wearing of masks by surgeons, nurses, and attendants during the performance of surgery and at *all dressings of open wounds* At the time of the armistice, in 1918, it had already been noted by the British that many of the nurses and orderlies were carriers of streptococci in their throats<sup>10</sup>

When dealing with the traumatic wound, one can add little to Reid's dictum, that "it is the duty of the surgeon to remove all foreign bodies or dead or devitalized tissues, which are excellent encouragement to the growth of bacteria"<sup>13</sup> The crux of the debridement is the removal of *all* dead and devitalized tissues, debris, and foreign bodies Bacteria increase in debris and necrosis, and a blood clot in such wounds soon becomes an infected slough In the initial treatment of these wounds there may be deep pockets, as about a fracture, in which wound secretions and blood may puddle This, and also the deleterious pressure effects of such an hematoma, may be prevented by providing dependent drainage for one to three days All of this was clearly stated by Churchill in a letter on Wound Management

"The keystone of successful wound management is the initial surgical operation When this is performed correctly the complications of infection are absent or minimal and secondary suture may be carried out promptly and successfully

"Use fine hemostats Use the finest ligatures compatible with the procedure Include the smallest amount of tissue in ligating a bleeding point Do not repeatedly bite the wound with tissue forceps Sponge

gently with pressure instead of wiping. *Remaining devitalized tissue produced by the missile or by the surgeon must slough before the wound can be closed by secondary suture*

"Large wounds in regions of heavy muscles particularly when complicated by comminuted fracture require especial care. The depths of these wounds must be opened by a long incision with counterincision if necessary to allow free drainage of blood and tissue that may not be identified as dead at the time of debridement."<sup>21</sup>

Bactericidal agents are always harmful to the tissues when used in wounds. In infections, however, the harm to living cells may be outweighed by their value in the control of the infection and it is obvious that in the treatment of such infections some of the principles of surgery of wounds may have to be sacrificed temporarily in order to save life.<sup>13</sup> In World War I more than twenty different antiseptics were used in the ever present hope of finding some means of sterilization and selective chemical debridement of wounds. Some have been discarded altogether and the others have dropped into their correct position as adjuvants in the control of established infection.

When the bacteriostatics, the sulfonamides and penicillin and streptomycin, are employed, it should be realized that whatever their action, it is purely ancillary to, and never can replace, surgery. In the presence of slough, dead tissue and infected clot their action is nil. Administered systemically they are of great value in preventing the extension of infection and in the preparation of patients for wound revision and other surgery.

**General Factors** The general factors that enter into the repair of wounds and that are under the control of the surgeon are hydration and electrolyte balance, circulation and the blood picture, nutrition and the vitamins.

**Hydration** There is an intimate relationship between hydration, blood volume and circulation and unless the complete blood picture is considered in relation to, and corrected in accordance with, the existing state of hydration, serious mistakes in treatment may occur. Furthermore, what is considered normal hydration for certain cases, such as an abdominal wound complicated by peritonitis, might well result fatally in a wound of the thorax with disturbed cardio-respiratory physiology. Over-hydration must be avoided both because of the harm it may do to the patient generally, and specifically, because it interferes

with wound healing and prolongs the initial period of lag. Proper balance in the electrolytes should likewise be maintained and caution exercised not to overload a patient with normal saline solution, for instance, when he has no need of added chlorides, since this will eventually lead to edema and over-hydration due to the retention of the fluids in the tissues because of the excessive salt intake.

*The Circulation and the Blood* It is essential that the circulation be competent in order to assure wound repair as edema and anoxia both impede it. Severe anemia produces a tissue anoxia, and with the ready facilities for hematocrit, hemoglobin, and plasma protein determinations now available to us by the copper sulfate method the blood status should be known and followed and any deficiencies promptly remedied by transfusions, both preoperatively and postoperatively. Anemia will almost always be present when one is dealing with major trauma, and, quite apart from the problem of adequate resuscitation, blood will probably also be required to overcome it.

*Nutrition* Nutrition profoundly influences the repair of wounds. A high protein diet favors and a high fat diet retards it. Large amounts of protein are necessary at first and in the presence of infection with copious exudate and sepsis the dangers of hypoproteinemia are well known. In the diabetic the problem of diet assumes large proportions in its relation to the repair of tissues and infection. Of recent years nutrition has taken on added significance because of the large numbers of people on a starvation or near starvation ration with evidence of early famine edema and avitaminosis. A few sentences may be quoted from a report of conditions in a Prisoner of War camp in Luzon:

"And above all, we encountered malnutrition. Its alleviation took precedence over all but the most dire surgical emergencies, and the associated anemia and hypoproteinemia handicapped the response to the most ideal surgical treatment \* \* \* \* The healing of open wounds and ulcers progressed only when the nutritional state of the patient improved."<sup>22</sup> Obviously the best way of providing adequate nutrition is by an abundant and varied diet. Where this is not possible, however, best use must be made of the available tools. Thus transfusions, plasma, protein hydrolysates by vein or tube, intravenous glucose and tube feedings will be of great value until a normal diet can be taken. The important thing is to continue some form of nutrition, for saline and glucose infusions alone are insufficient.

*Vitamins* What has been said about nutrition applies also to vitamins. We are well aware of the role played by vitamin C in repair of wounds and the needs of the body for A, B, D, and also K under certain conditions. Many people on their usual diets may show some degree of vitamin deficiency. The original C-ration as supplied to the Army in 1942 and 1943 was notably low in vitamin C. So in the initial stages of wound repair adequate vitamin therapy must be provided to assure healing.

### SUMMARY

Seven hundred years ago the principle that wounds should heal *per priam* was enunciated by Ugo of Lucca. After an hundred years, however, this heretical opinion was overridden and surgery went back to the Galenical theories of *pis laudabile* and polypharmacy, not to emerge again until the last half of the nineteenth century under the leadership of Baron Lister, who firmly established antiseptics and then asepsis.

In 1891 William S. Halsted taught the modern principles of wound healing.

Our present conceptions are based upon his teachings. The points in the surgery of the wound and its repair are sharp dissection, gentle handling of tissues, complete hemostasis, maintenance of blood supply, avoidance of tension and strangulation of tissues, obliteration of dead spaces, the use of fine ligatures, the *excision of all devitalized or dead tissue and sloughs*, the removal of foreign bodies, and the application of a nonconstrictive dressing of even pressure.

In the cleanly prepared wound bactericidal agents are not only not indicated but do harm rather than good.

It is not necessary to "stimulate" healing. This will progress normally provided a wound is properly prepared, left clean, and dressed with a simple supportive dressing, and provided the patient is maintained in a normal balance as to hydration, blood picture, nutrition and vitamins.

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BULLETIN OF  
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DECEMBER 1946

INDICATIONS FOR SURGERY IN THE  
TREATMENT OF GASTRIC AND  
DUODENAL ULCERS\*

J WILLIAM HINTON

VISITING SURGEON BELLEVUE HOSPITAL

THE end results from both medical and surgical treatment of ulcers are frequently poorly understood by both the internist and the surgeon because they lack the opportunity for a long period of observation of the results of both methods. The life cycle of an ulcer is long and the flare-ups of pain and massive hemorrhage cause the patient to become discouraged or alarmed and frequently he seeks the advice of another physician, or more likely a surgeon, as the one to offer permanent relief. Having spent over 18 years in the Ulcer Clinic of the 4th Division at Bellevue Hospital and 7 years in the Ulcer Clinic at Post-Graduate I believe I can see more clearly the advantage of both methods of treatment and I shall present my deductions today.

The patient suffering from a gastric ulcer is more likely to be advised operation than a patient with a duodenal ulcer. The danger of malignant degeneration is the motivating factor in the choice of surgery for most cases of gastric ulcer. The incidence of the development of

\* Presented before the Friday Afternoon Lecture Series of The New York Academy of Medicine  
March 8, 1946

malignant changes is quoted variously as 1 per cent to 70 per cent. The pathologists have had difficulty in the differential diagnosis of some of the gastric lesions as Cole<sup>1</sup> illustrated 10 years ago. These are the same cases which the roentgenologist, the gastroscopist and the clinician have difficulty in accurately diagnosing. The clinical course of an ulcer of the stomach has a most important bearing on the indications for operation. In some cases it is difficult to distinguish a gastric ulcer from a carcinoma. In 85 per cent of our cases<sup>2</sup> we could not be certain of the diagnosis and an immediate operation was advised, but in this group 75 per cent were found to be ulcers upon histologic study following sub-total resection. This does not prove that a gastric ulcer becomes a carcinomatous lesion, but in a small group of cases we have no accurate method of differentiating between the two lesions. My views on this point coincide with the opinion expressed by Palmer<sup>3</sup> that the existence of carcinomatous degeneration in a benign ulcer remains to be proved conclusively. The United States Bureau of Census states that there were 6,390 deaths from gastric ulcer in 1943 and 2,943 deaths from duodenal ulcer. These figures are hard to reconcile since gastric ulcers constitute only about 10 per cent of the total number of ulcers encountered. In our clinic at Bellevue Hospital we found<sup>4</sup> that of 1,256 ulcers 89 per cent were duodenal and 11 per cent gastric.

In the stomach clinic of the 4th Medical and Surgical Divisions at Bellevue Hospital, which is entering its 19th year, we have adopted the policy that a gastric ulcer will respond to medical management as satisfactorily as will a duodenal ulcer, and in most instances it is easier to heal a gastric ulcer than a duodenal ulcer on a dietary regimen. The mistakes in following such a policy are few compared with the mortality from sub-total resection of gastric ulcers in the hands of the average surgeon. Any one doing a reasonable amount of gastric surgery can have a low mortality. The author has just reported<sup>5</sup> 162 cases of primary duodenal ulcer with 6 deaths, or 3.7 per cent mortality, and 85 cases, 22 per cent of which were gastric ulcers in which a sub-total gastrectomy was performed, with a mortality of 3.5 per cent.<sup>6</sup>

From 1920 to 1944 inclusive there were 806 ulcer admissions on the Medical and Surgical services of Post-Graduate Hospital 112 of which were gastric ulcers, 13.8 per cent of the total. It is interesting to review these cases as they came under the care of a large number of doctors during the 25 year period. Private cases are not included in this dis-

cussion In the early part of this period local excisions and gastroenterostomies were performed for gastric ulcers In 43 cases sub-total resections were done, with 11 deaths or a 25.5 per cent mortality Thirty-three gastric ulcers were treated medically, with no deaths, but one of these patients was subsequently admitted with carcinoma one year after the first admission In reviewing the history of this case it would seem that the patient had a carcinoma originally There were 12 cases of gastric carcinoma in which there was a question of its arising on a pre-existing ulcer These cases are included in the 112 ulcer cases and constitute 10 per cent of the total gastric ulcer admissions over the 25 year period This is not high when we remember that gastroscopy was not employed in the early cases and our roentgen studies were not as accurate as they are now

In two cases it might be argued that the ulcer developed into a carcinoma One of these patients, a man 45 years of age, was admitted in January of 1925 with a five weeks' history of upper abdominal discomfort The gastrointestinal x-ray series revealed a gastric ulcer on the lesser curvature in pars media and a Balfour excision and a gastroenterostomy were done The patient was re-admitted in February 1941 with a carcinoma of the stomach which involved a pyloric portion on the greater curvature Whether this carcinoma arose from the original ulcer or whether it was a separate growth cannot be proven, but it would seem that after a period of 17 years, in all probability the carcinoma was not related to the original ulcer The second patient was a man 48 years of age admitted in January 1933 with an 8 year history of stomach trouble He was found to have a pyloric ulcer and a gastroenterostomy was performed In January 1939 he was re-admitted with an inoperable pyloric ulcer These two cases, and the medically treated patient re-admitted with carcinoma of the stomach one year later, which was apparently an undiagnosed primary carcinoma, constitute the only clinical proof we have of the danger of carcinomatous degeneration

The interesting question is whether sub-total gastrectomy should be so freely recommended in cases of gastric ulcer to prevent malignant degeneration when the procedure in the hands of the average surgeon carries such a high mortality In this group of cases covering a 25 year period the 25.5 per cent mortality comes nearer to approximating the mortality in the average hospital than do figures given from large medical centers which represent the experience of a small group of highly

trained gastric surgeons

The decision as to conservative management or operative intervention in duodenal ulcers is usually dictated by the probability of operative mortality if surgery is advised

Duodenal ulcers, if diagnosed early, will respond very satisfactorily in most instances to a medical regimen. A small percentage, even with adequate medical care, will become intractable or recalcitrant. The great difficulty encountered by both internist and surgeon is in differentiating between exacerbations of a chronic duodenal ulcer and intractability which necessitates operation. The patient with a chronic duodenal ulcer may become discouraged during a period of exacerbation and seek the advice of a surgeon. Frequently the surgeon mistakes an exacerbation for chronic intractability and if an operation is performed the end results will often prove disappointing, while the end results from sub-total resection for intractability prove most gratifying.

The duodenal ulcer which penetrates the posterior wall and becomes adherent to the pancreas can no longer be treated medically and becomes a surgical problem. Also, any duodenal lesion which has completely penetrated the wall of the duodenum and is adherent to an adjacent viscus, whether it be the gall bladder, the liver or the duodeno-hepatic ligament, is a true surgical problem and sub-total resection should always be performed with removal of the ulcer *in toto*. Gastroenterostomy will prove most disappointing in this type of case. In a previous review<sup>7</sup> of gastroenterostomies for intractable duodenal ulcers we found only 24.5 per cent of cures in 106 cases followed for 7 1/2 years. Of course if a gastroenterostomy is performed early, before the complications of the long standing ulcer have arisen, the results will be much better, but these patients can obtain symptomatic relief on an adequate medical regimen.

Continuous pain with the x-ray findings of a penetrating lesion in the duodenum will suffice to differentiate between the intractable ulcer necessitating operation and the exacerbation which will subside with adequate medical care. However, there is one type of duodenal ulcer which is difficult to diagnose and which will not respond to a medical regimen, and that is the ulcer on the pyloric sphincter. This ulcer causes extreme pain and frequently the gastrointestinal series will show, not a true penetrating lesion but a marked pylorospasm. In this instance a sub-total resection should be done with removal of the lesion. This type

of ulcer is similar to a fissure in ano, and, as is well known, the anal fissure causes pain out of proportion to the pathology found

In the past 13 years I have not performed a gastroenterostomy for any type of ulcer. The so-called pyloric obstruction without pain will always respond to gastric lavage, anti-spasmodics, and dietary management. There are cases of pyloric obstruction which will not respond to a medical regimen, but these patients have a penetrating ulcer with associated pain. Gastroenterostomy in this type of case will prove most disastrous because the active duodenal ulcer remains unhealed and gastrojejunal ulcer is a frequent sequela.

Massive hemorrhage always presents a problem in the treatment of peptic ulcer. Conservative treatment in these cases is attended with a definite mortality.

In 135 cases of massive hemorrhage treated on the 4th Division at Bellevue Hospital from 1928 to March 1937 inclusive there was a 12 per cent mortality under conservative treatment.<sup>8</sup>

Hospitals without an active ambulance service see very few patients with exsanguinating hemorrhages because of the severity of the condition, and with the alarming feature of vomiting large quantities of blood, an ambulance is usually called immediately. The patient admitted with a severe gastric hemorrhage should have a blood grouping immediately and a transfusion started. Hemorrhage is caused either by a venous ooze or by erosion of a large artery. Most bleeding ulcers are duodenal, since 90 per cent of all ulcers are duodenal. A gastric ulcer may have a large artery at its base but massive hemorrhage from a duodenal ulcer results from erosion of the superior pancreatico-duodenal artery or one of its large branches by the ulcerating process. An arterial hemorrhage will prove fatal unless controlled while a venous ooze will respond to conservative treatment.

Surgery is employed occasionally as a life-saving measure, but these instances should be few in a large series of cases. Most massive hemorrhages can be controlled by transfusion and conservative measures. The problem is to determine which case will continue to bleed. We have used the transfusion test as the best means of determining which patients have arterial hemorrhages necessitating operation as against those with venous ooze. A continuous transfusion is given by the indirect method and if after receiving 1500 to 3000 cc. of blood the patient remains in shock, it is very likely that the superior pancreatico-duodenal artery is



## OBSERVATIONS ON THE DYNAMICS OF THE SYSTEMIC CIRCULATION IN MAN\*

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THE dynamics of the systemic circulation is a very large and complex subject, involving not only blood flow as a whole, under the various existing levels of vascular pressure throughout the circuit, but including also all the local and regional conditions of pressure and flow, each with its own independence of action, yet each influencing and itself a part of the adjustment of the whole system.

My discussion this evening will not attempt to cover this field but will be restricted to the circulation as a whole, in man, that is, the behavior of blood in the systemic great vessels and the heart. It will be concerned particularly with the contributions to this subject which have been made during the last four years by the technique of right heart catheterization.<sup>1</sup> Dr. Cournand's paper, which follows, will describe the contributions which have been made similarly to the knowledge of the pulmonary circulation.

The chief methods used have been, first, the determination of cardiac output, by the familiar Fick principle<sup>2</sup> and second, the continuous recording of pressures, in heart and great vessels, by optical registration.<sup>3</sup>

The so-called direct Fick principle depends upon direct determination of three values, oxygen in arterial blood, oxygen in mixed venous blood, and total oxygen intake per minute. Cardiac output is obtained by dividing oxygen intake per minute by the arteriovenous oxygen difference. This method of cardiac output determination is now generally accepted as the most reliable in human subjects.

As is well known, there has been for many years a controversy over the value of resting cardiac output in man. Earlier methods gave values of 5 to 6 liters per minute. In the last decade, the accepted foreign gas methods gave as a normal average 2.2 liters per square meter of body surface, or between 3.5 and 4.0 liters per minute.<sup>4</sup>

\* Under a grant from the Commonwealth Fund.  
Read at the Stated Meeting of the New York Academy of Medicine, March 7, 1946.

TABLE I

BLOOD FLOW THROUGH VARIOUS ORGANS AND  
REGIONS OF THE BODY, IN MAN AT REST

Brain	900 cc/min
Kidney	1300 "
Liver	1300 "
Extremities	1800 "
	5300 "
Lungs (cardiac output)	5400 "

By the catheterization technique, in the hands of several independent investigators,<sup>2 5 6</sup> the average cardiac output of the normal subject at rest is approximately 5.4 liters per minute, or 3.1 liters per square meter of body surface.

As pointed out by Hamilton,<sup>7</sup> this figure fits better with that obtained when one adds together the blood flows through special organs and regions of the body. This is indicated in Table I. The cerebral blood flow figure is that of Schmidt,<sup>8</sup> renal flow obtained by Smith's renal clearance method,<sup>9</sup> hepatic flow by an interesting method developed by Bradley,<sup>10</sup> in which he catheterizes one of the hepatic veins, and measures hepatic clearance or removal from the blood of bromsulfalein. The agreement in the table is not perfect as no account is taken of such regional blood flows as the coronary, thyroid, adrenal, and intercostal, but it is reasonably good.

Another controversial question has been that of cardiac output alteration with change of posture. Earlier investigators using indirect re-breathing methods found cardiac output depressed in the sitting or standing as compared with the recumbent position. With the ethyl iodide and acetylene methods no significant difference was found.<sup>4</sup> McMichael and Sharpey-Schaefer<sup>6</sup> using right heart catheterization, found in fourteen subjects unequivocal evidence that the cardiac output is less in the upright than in the recumbent position, the average decrease being 34 per cent.

When both total flow and initial and final pressures are known in a fluid-filled system of tubes, it should be possible to describe the resistance along the system. The circulation of the blood, however, is

TABLE II—NORMAL CIRCULATION

	<i>Rest</i>	<i>Moderate Exercise</i>
Pulse Rate, per min	60	150
Cardiac Output, liters/min	5.4	20
Arterial Pressure, mm Hg	120/80	160/95
Venous Pressure (arm), mm Hg	4	10
Right Auricular Pressure, mm Hg	2	2

extraordinarily complex. Blood is not a homogeneous fluid but a suspension, in the smallest capillaries each cell often distending the vessel as it moves along. The flow is pulsatile in the arteries, steady in the veins. The channels of flow are elastic, arteries, capillaries and veins having different distensibilities, and being subject to large and unpredictable nervous or vasomotor effects. No law of flow has been devised that will describe so complicated a system.

There is, none the less, some usefulness in the general concept of peripheral resistance. This is, essentially, the average rate of fall of blood pressure around the circuit, per unit of blood flow. It is expressed as a simple ratio, mean arterial pressure divided by cardiac output. The general significance of this ratio is obvious: a high arterial pressure and a small cardiac output means a high peripheral resistance, a low arterial pressure with a large output means a low resistance. Table II gives some normal figures of the circulation at rest and in moderate exercise. The peripheral resistance at rest would be represented by mean arterial pressure, about 90 mm Hg, divided by cardiac output 5.4, or a figure of 1.4; in exercise, a mean pressure of, say, 120, divided by 20, or a figure of 6, indicating the extent of vasodilatation in exercise. In current usage, the term is usually expressed in dynes per  $\text{cm}^2$  per second, which gives normal values between 1000 and 1500.

An interesting study in this connection is that recently carried out in Dr. Cournand's laboratory, in collaboration with Drs. Chasis and Goldring, the measurement of blood flow and pressures in five cases of essential hypertension both before and following bilateral sympathectomy. The results are summarized in Table III. The patients had high

TABLE III

EFFECT OF BILATERAL SYMPATHECTOMY UPON CARDIAC OUTPUT AND PERIPHERAL RESISTANCE IN 5 CASES OF ESSENTIAL HYPERTENSION

	Body Surf Area	Mean Art Blood Press mm Hg	Cardiac Output			Periph Resist	1-V Diff cc / lit	O <sub>2</sub> Intake cc/min /sq m	Pulse Rate
			per minute lit	lit / sq m	per beat cc				
Average before operation	1.68	160	5.70	3.39	70	2250	41	138	82
Average after operation	1.60	135	5.52	3.45	64	1960	38	131	87

TABLE IV

VARYING EFFECTS OF METHEDRINE ON THE CIRCULATION

Subject	Time	Pressures mm Hg				Cardiac Index liters	A-V Diff	Periph Resist	Pulse Rate
		Arterial (femoral)	Right Syst	Ven- tricle Diast	Right Auricle				
F K Female, 33, normal	0	127/65	25	4	—	2.47	3.9	1760	60
	0	125/62	21	1	—	2.34	4.0	1770	58
	4'	Methedrine, 30 mg intravenously							
	18'	209/94	43	5	—	—	—	—	—
J F Male, 30, lac scalp, 15% blood loss, acute alcoholism	0	195/89	65	6	—	2.64	4.2	2440	62
	0	63/34	—	—	2	2.81	5.0	620	59
	7'	Methedrine, 30 mg intravenously (6 hrs after injury)							
	36'	95/53	—	—	—	—	—	—	—
	134'	98/56	—	—	3	3.98	3.9	700	100
J K Male, 53, phlebotomy, - 20% of blood volume	0	91/50	—	—	—	3.98	4.1	630	66
	0	58/37	—	—	1	1.81	8.1	1410	104
	5'	Methedrine, 30 mg intravenously							
	10'	80/50	—	—	—	—	—	—	115
	58'	86/55	—	—	—	—	—	—	140
	58'	87/56	—	—	—	1.73	7.2	2330	133

blood pressures but normal cardiac outputs before operation. Sympathectomy caused no change in output, the result being solely that of reduction in arterial pressure, and correspondingly, in peripheral resistance.

The reverse change is seen in the effects of the sympathomimetic drug methedrine on the normal circulation. As Table IV shows, there is a sharp rise in arterial, also in right ventricular pressure, but no change in cardiac output, peripheral resistance increasing from 1770 to 2440.

Quite different is the response to this drug in a patient in moderate shock, who was also acutely alcoholic, with the characteristic vasodilatation and hypotension produced by alcohol, also shown in Table IV. In this case methedrine brought about an increase in both arterial pressure and cardiac output, together with a striking clinical improvement. This illustrates a principle often overlooked, that a drug may have quite a different effect under pathological conditions from what it does under normal conditions.

Before considering pressure relations in the great veins, leading up to, and including intracardiac pressures, one should perhaps emphasize again the primary fact that while the heart is an effective pump, it can eject only as much blood as reaches it by way of the venous return. This physiological principle was established many years ago by Krogh, Yandell Henderson, and others.

The pressures in auricle and ventricle in the normal cardiac cycle have been extensively studied in dogs by Wiggers and others. Such pressures in man are similar, as recently demonstrated by Bloomfield et al.<sup>3</sup> Figure 1, A is a continuous recording of auricular pressure through a number of cardiac cycles, in a normal subject. The electrocardiogram is at the top of the record, the arterial pressure next (obtained from an indwelling needle in the femoral artery), and below this the right auricular pressure. As recorded here, the first event in the cardiac cycle is the P-wave of the electrocardiogram, followed very shortly by the beginning of the auricular pressure rise caused by auricular systole (line 1 on tracing). Auricular systole, some 4 mm or 5 mm in amplitude, rises to its peak and declines (1 to 2 on tracing). The subsequent small nick, or momentary rise in the auricular record (2 to 3 on tracing) corresponds to the onset of ventricular systole. This is found on animal records and is generally agreed to be the quick bulging backward of the tricuspid valve. The subsequent sharp drop (beyond line 3) in

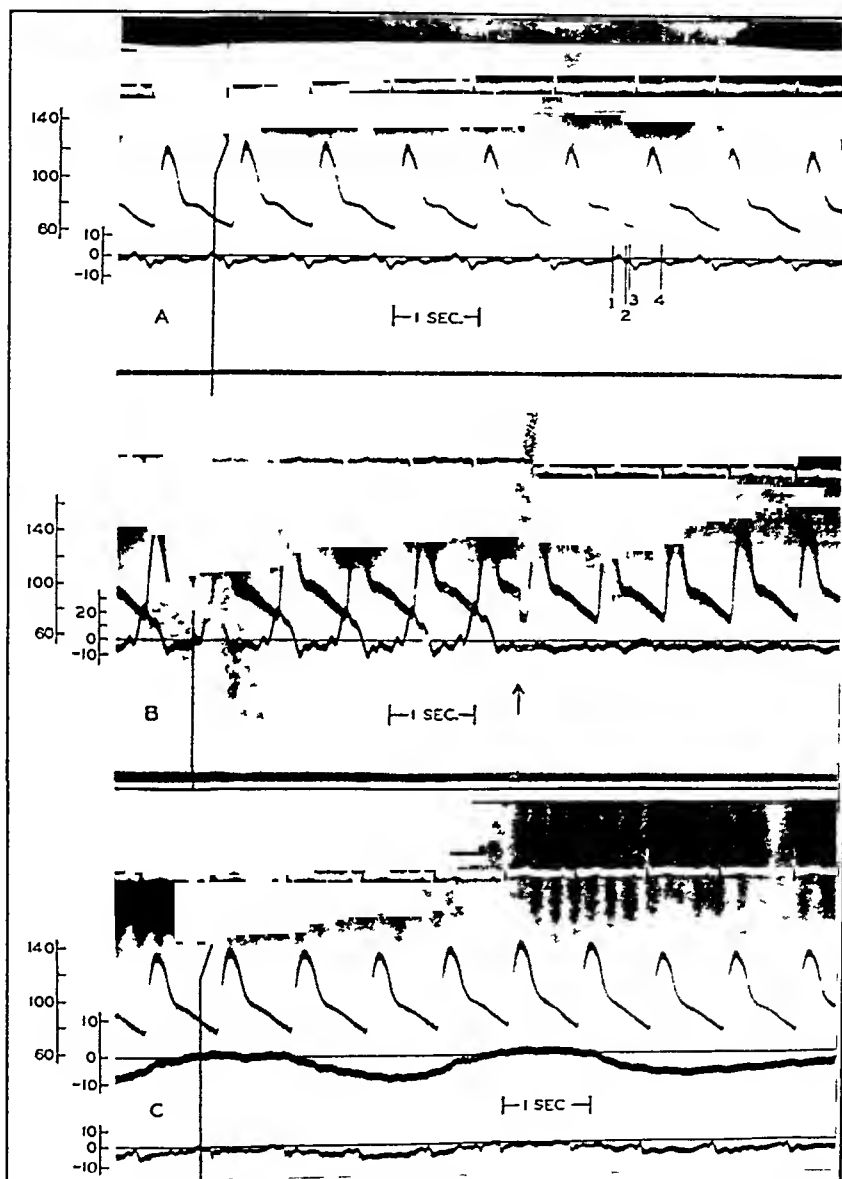


Figure 1 Pressure tracings in normal human subjects Section A, from above downward electrocardiogram, femoral arterial pressure, right auricular pressure Vertical line indicates identical times on the three tracings For explanation of points 1, 2, 3, and 4, see text Section B electrocardiogram, femoral arterial pressure, right ventricular pressure in first half, right auricular pressure beyond arrow Section C similar to A, except for intrapleural pressure tracing (inspiration up, expiration down) between tracings of femoral artery and right auricle

auricular pressure is due to the "descent of the base" of the heart, the whole tricuspid region moving downward as ventricular contraction is completed with upward ejection of blood into the pulmonary arteries. The subsequent steady rise in auricular pressure up to line 4 is due to venous inflow, with tricuspid valve still closed. At line 4 ventricular relaxation has progressed so that the tricuspid valve opens, with another drop in auricular pressure. After this, pressure builds up again in the common auricular-ventricular chamber from inflowing venous blood, until auricular systole starts a new cardiac cycle.

In the first half of Figure 1, B the pressure record from a normal right ventricle is shown, together with simultaneous electrocardiographic and arterial pressure tracings. The vertical line, marking the peak of auricular systole (just as in Figure 1, A above), shows that auricular systole causes a small upward wave in ventricular pressure. This is to be expected since the tricuspid valve is open and auricle and ventricle form a common chamber. Next comes the sharp rise due to right ventricular contraction, reaching a maximum systolic pressure in the lesser circuit between 18 mm and 30 mm Hg. The form of the summit of the ventricular pressure curve is variable from one subject to another, sometimes irregularly peaked, as here, sometimes flattened or rounded. Whether these represent genuine pressure variations or are artefacts of recording, is not known.

Ventricular relaxation, as shown, is also rapid, resulting in a drop of pressure ending in a "dip" which is practically synchronous with the auricular dip seen after line 3 in Figure 1, A above. The tricuspid valve being open, auricular and ventricular pressures then rise together, up to the next auricular systole.

At the arrow in Figure 1, B, the catheter tip was withdrawn into the right auricle. The subsequent auricular tracing is a rather poor record technically.

Figure 1, C shows also a record of respiration, the patient breathing in this instance somewhat rapidly and deeply. The effect of this on both the amplitude and basic pressure level of the auricular tracing, is well brought out.

Mean pressure in the right auricle in most normal subjects varies between a level 2 or 3 mm Hg above to the same amount below an arbitrary zero level, this latter being taken on these records as 5 cm below the angle of Louis, with the subject lying recumbent.

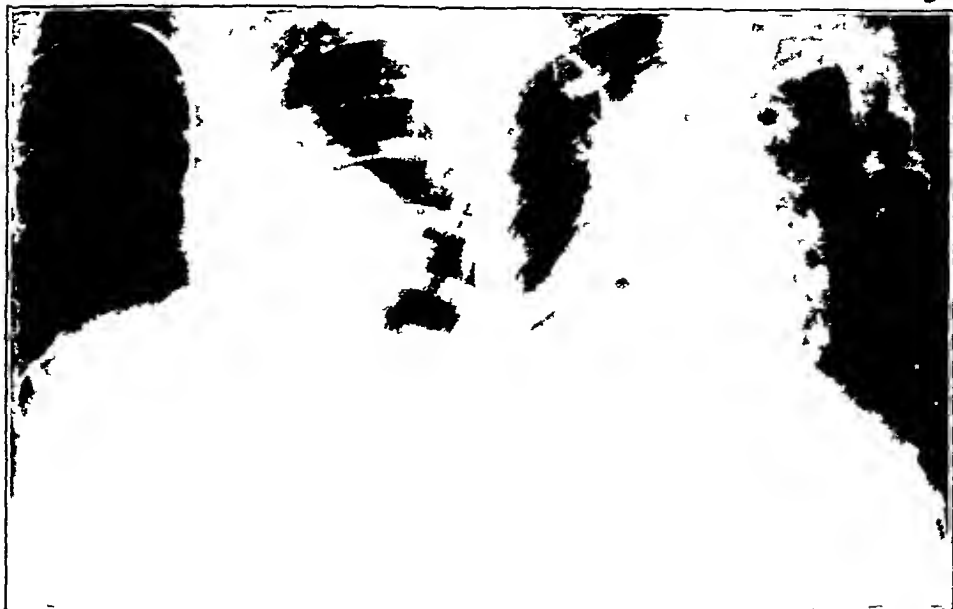


Figure 2 Catheter passed into right auricle, right ventricle, through septal defect, and around aortic arch

Such is a brief description of the pressure changes within the right heart during the cardiac cycle

On the venous side of the circulation, one other normal phenomenon may be mentioned, namely, the pressure difference or pressure gradient between arm vein and right auricle. This difference is variable but averages about 40 mm of water.<sup>11</sup> This arm to heart gradient, as Ferris has shown,<sup>12</sup> is due largely to the collapse of the larger peripheral veins in the resting state.

Variations in right ventricular pressures in physiological and pathological conditions are concerned more immediately with the pulmonary circulation and will be discussed by Dr Cournand in the succeeding paper.

One additional tracing might perhaps be shown, a pressure record in a human aorta. This was a patient with septal defect catheterized recently by Dr Cournand, the catheter passing through the defect and on around the aortic arch. Figure 2 shows the catheter in the aorta, and Figure 3 the intra-aortic pressure tracing.

Peripheral circulatory failure, or shock, in its various forms has received intensive study during the war, by these as well as other meth-



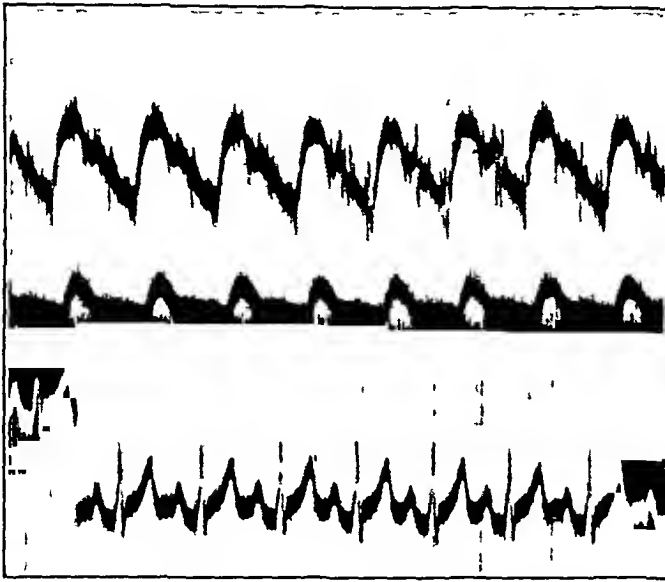


Figure 3 Intra-aortic pressure tracing (above) from case shown in Figure 2. The record is distorted by vibrations. Below is a femoral artery tracing, much damped, and below this the electrocardiogram.

ods, and only the briefest review is indicated in this discussion. Perhaps the most significant addition to our concept of peripheral circulatory failure is that there are a number of specific types, each with its own pattern of circulatory disturbance.<sup>13</sup>

The standard form, so to speak, of secondary shock is that produced by skeletal trauma or hemorrhage, presented in chart form in Figure 4. Here trauma and hemorrhage are compared with the normal in blood and red cell volume, cardiac output, auricular pressure, arterial pressure, and peripheral resistance. The basic loss here is whole blood, with red cells further down than serum, the low blood volume leading to decreased venous return, decreased cardiac output, decreased arterial pressure.

Figure 5 shows an arterial pressure tracing in advanced shock, compared with the normal. The low systolic level, and collapsing quality, are apparent, indicating an essentially empty vessel. Figure 6 shows an arterial and a right ventricular tracing after acute blood loss, with gradual recovery over several hours following intravenous fluid. The small ventricular complex is indicative of poor cardiac filling.

The shock seen in severe burns has quite a different pattern (Figure 7). There is of course hemoconcentration, loss of blood volume, and

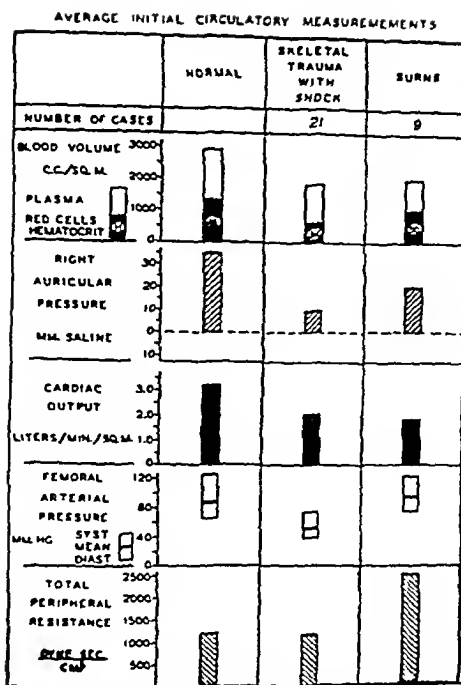


Figure 4 Chart showing chief dynamic changes in the circulation in traumatic and hemorrhagic shock

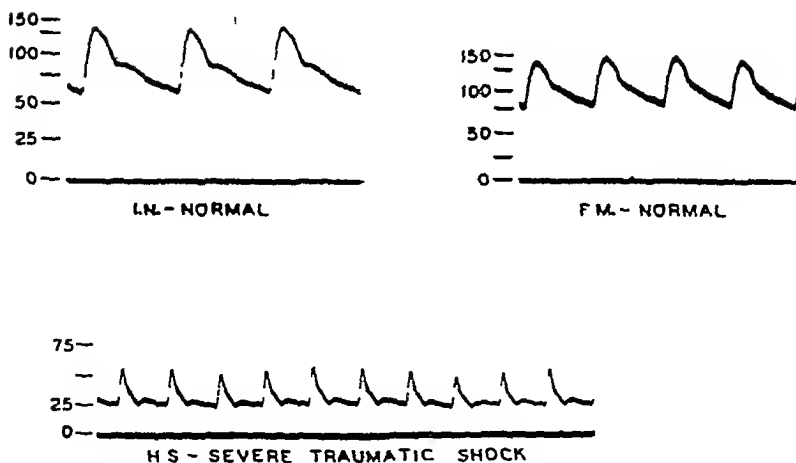


Figure 5 Femoral artery pressure tracings in normal subjects and in shock

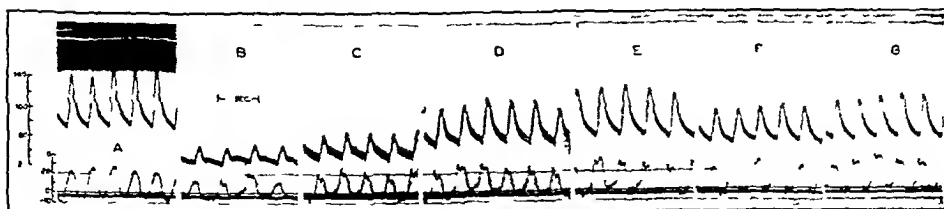


Figure 6 Tracings from femoral artery and from right ventricle in a normal subject before and after a large phlebotomy A = before B = immediately after patient was paled and in shock Cardiac output was 40 per cent of normal C, D, E, and F = progressive stages in recovery during and following an intravenous infusion of gelatin solution G = 1 hour after phlebotomy, cardiac output then 95 per cent of normal

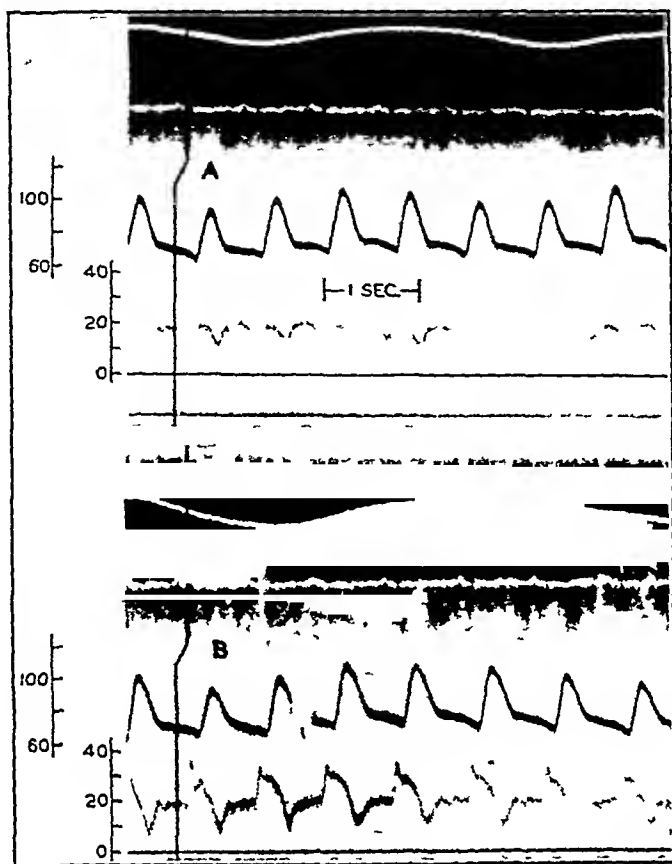


Figure 8 Pressure tracings in a patient with right-sided failure (constrictive pericarditis) Upper curve, pneumograph, next electrocardiogram, next femoral artery pressure, at bottom pressure in right auricle (Section A) and right ventricle (Section B)

Intracardiac pressure records bring out clearly the pressure abnormalities in congestive heart failure. Figure 8, A gives the auricular pressure tracing in a patient with right-sided congestion (This particular case was one of constrictive pericarditis). The contrast to the normal record (Figure 1, A) is apparent. The basal or diastolic level of auricular pressure is of course elevated, around 20 mm Hg or 260 mm of saline. Auricular systole is only faintly recorded in this case. With the descent of the base early in ventricular systole there is a marked drop in auricular pressure, followed by a rapid rise again, as blood comes in from the distended great veins to fill the auricle. With ventricular relaxation, at the opening of the tricuspid valve, there is again a sharp drop in auricular pressure, followed by a rapid rise. The whole picture is that of a dis-

tended chamber under increased pressure, with two momentary periods of pressure release. The W-shaped auricular pressure curve is characteristic of the congestive state. Figure 8, B gives the corresponding right ventricular tracing. The sharp "diastolic dip" with ventricular relaxation is again evidence of a distended (auricular) chamber, followed by sudden release of pressure, followed in turn by rapid filling both of auricle and of ventricle and return to high venous and intracardiac pressure.

A further problem of interest is the mechanism of development of edema in congestive heart failure. The original theory of Starling held that "backing up" of pressure in the great veins led, by way of retarded blood flow through the bone marrow, to increased blood volume, the systemic venous bed thus becoming distended with fluid, which escaped into the tissues. Warren and Stead<sup>17</sup> found, in resting cardiac patients, that with increased fluid intake, blood volume increased before any rise occurred in venous pressure. More recently, Merrill<sup>18</sup> has shown, both that renal blood flow is greatly decreased (to one-third normal) in congestive failure, and that there is a good correlation between renal blood flow and cardiac output, but no correlation between renal blood flow and venous pressure. Stead and his colleagues advance the theory that edema in congestive failure is primarily a renal failure to excrete salt and water, caused by a cardiac output inadequate to body needs, and secondarily a decreased renal blood flow. Landis<sup>19</sup> stresses the importance of considering venous pressure in cardiacs during stress as well as at rest, and shows that in dogs with experimentally damaged hearts increasing the load on the heart will send it into frank congestive failure with abnormally increased venous pressure, whereas at rest no failure was demonstrated. Still further evidence is probably needed to decide this question.

There is one form of heart failure which can be diagnosed rather accurately by pressure tracings. This is congestive failure with tricuspid insufficiency. Figure 9 gives a tracing obtained in such a case. In this instance a double-channeled catheter was used, with one opening at the tip and the other about 10 cm back of the tip, so that when the tip is in the right ventricle, the second opening is in the auricle.

The characteristic feature here is that in the lower or auricular tracing the first dip of the W is absent. Instead of the descent of the tricuspid valve in early ventricular systole, blood spurts back into the

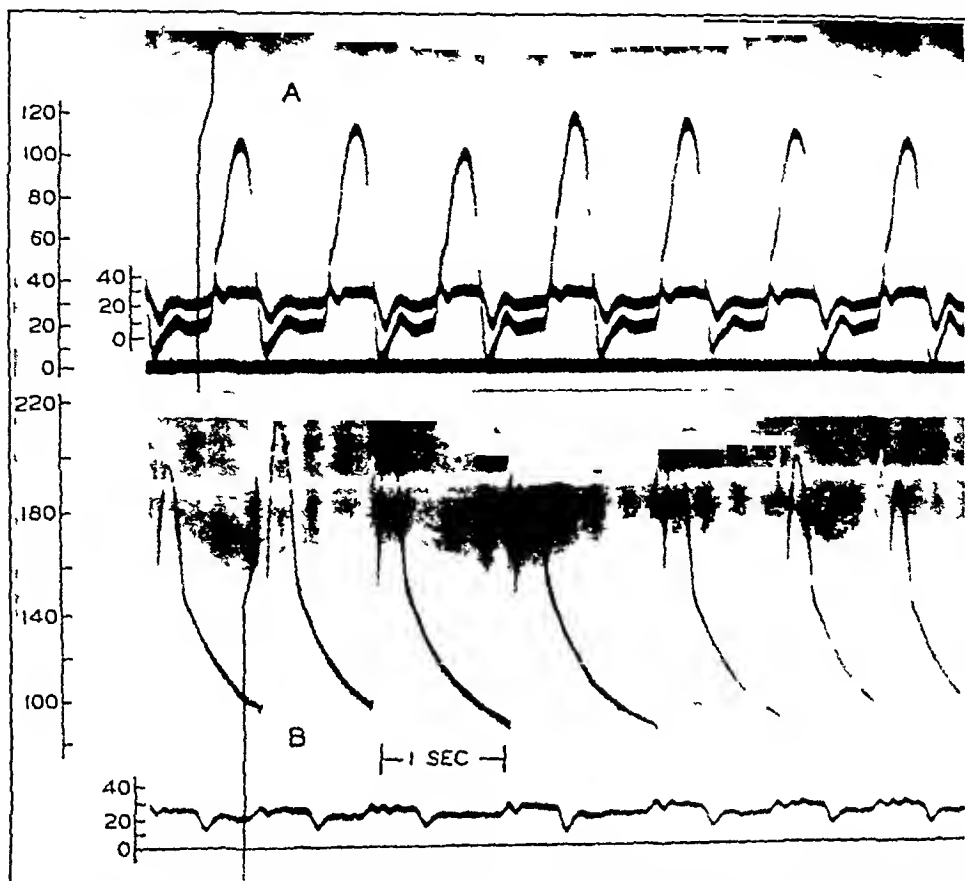


Figure 9 Simultaneous right auricular and right ventricular tracings (Section A) in a case of tricuspid insufficiency. See text

auricle, and auricular pressure continues unchanged or even rises slightly

So far as concerns the relation between the pressures in peripheral and central veins in congestive failure, it was found early in the course of catheterization studies,<sup>11</sup> that the normal gradient of 30 to 40 mm of water between arm and heart disappears, and in congestive failure, peripheral and central venous pressures become practically identical. This is probably due chiefly to venous distention, with larger channels of flow between arm and heart.

As a last observation I should like to mention some interesting work by McMichael and Sharpey-Schaefer<sup>20</sup> on the action of digitalis, or more specifically of intravenous digoxin on the pressure and output of the heart in congestive failure. It is of course well known, from a number of earlier investigations, that digitalis decreases both heart size and cardiac output in normal subjects, whereas in dilated failing hearts

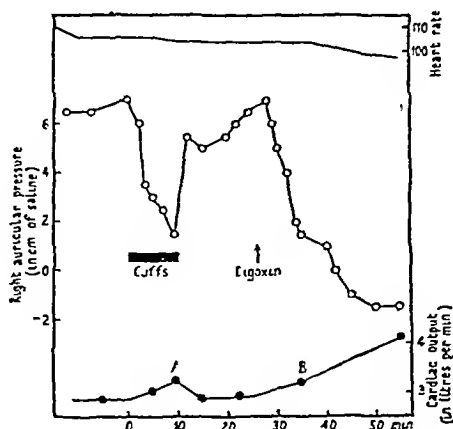


Figure 10 From McMichael and Sharpey-Schaefer (see text) Variations in heart rate, right auricular pressure, and cardiac output produced in a patient with congestive heart failure by cuffs on the extremities and by digoxin

digitalis decreases heart size but increases output McMichael confirmed this, but noted also a very marked and prompt drop in right auricular pressure as an early action of digoxin The whole effect was quite comparable to that of phlebotomy or of cuffs applied to the extremities, in these patients The chart of a typical case, from McMichael's paper, is shown in Figure 10 These results indicate a strong peripheral action of digoxin, opening up some as yet unidentified venous depots, permitting venous pressure fall, and thus relieving the congested heart It may be noted, however, that a direct action on heart muscle, by producing better cardiac emptying, would also decrease auricular pressure and increase cardiac output

This study of McMichael's with digitalis is a further illustration of the manner in which the effects of drugs on the circulation can be studied, and there would appear to be an excellent opportunity to investigate most of the rapidly acting cardiovascular drugs by this means

Summarizing these rather scattered observations, one may say that catheterization of the heart and the registration of pressures in heart and great veins have provided a number of new facts about the dynamics of the greater circulation in both normal and pathological states, that the nature of circulatory failure in various types of shock and in congestive heart failure has been somewhat clarified, that tricuspid insuffi-

ciency can be accurately demonstrated, and that with these techniques special opportunity appears to be offered for the study of cardiovascular drugs

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HUMAN BARTONELLA INFECTION AND  
AFRICAN SLEEPING SICKNESS \**(Field and Laboratory Experiences)*

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IT is particularly pleasant that the topic for this evening was delimited to tropical medicine, not alone because it is reassuring evidence of interest in a hitherto rather neglected subject, but chiefly because I believe that the pathology of tropical diseases has not received the attention it warrants from pathologists. Close collaboration between microbiologists, clinicians and pathologists is a commonplace in the fields of what, for want of a better term, we may call "Temperate medicine" but it is still lacking in the tropical field. I hope that this will soon be remedied, I take the invitation tonight as the expression of a similar desire on your part and so may it be. Ample opportunity for the study of tropical material will probably occur with the repatriation of the armed forces.

The French call tropical diseases, "Exotic Diseases," and with your leave I should like to apply this term which fits it so well to Bartonellosis. What could be more exotic, or curious if you prefer, than a disease which is contracted only in certain dangerous valleys, and then only at night, which causes deadly epidemics and kills in three weeks with a fulminating anemia, and which occurs nowhere else in the world but in a small area in South America? Add to this the fact that apparently an entirely different condition which is benign, wherein there is little or no anemia and which is marked by an eruption likewise such as is seen nowhere else on earth, actually is another form of the same disease, and you have an almost incredible story. It is not surprising that those who made the first reports on the subject were treated as medical Munchausens. This story happens to be correct. But the difficulties

\* Read January 25, 1945 at The New York Academy of Medicine before the New York Pathological Society.



inherent in proving its correctness will become apparent from a consideration of the history of the disease

The disease is now endemic in Peru and there is evidence to suggest that it has existed there for a very long period indeed. This evidence antedates the introduction of writing into Peru and is part archaeological and part linguistic.

The archaeological data derive from the pottery. Excavations have unearthed a great quantity of pottery in Peru. Many of these pots or "huacos" are anthropomorphic in design and executed with striking realism. Among these "huacos" some very clearly depict surgical operations, such as trepanation, as well as pathological conditions and deformities. Among these representations of diseased conditions verruga has been identified in pots executed by the Chimu peoples who flourished before the Inca conquest.

At the time the Spaniards arrived in Peru, the natives had a special term in their language, Keshua, to distinguish verruga from the common wart which it somewhat resembles. Written references begin with the Spanish. The very first group of Spaniards on their route south to the conquest of Peru in 1531 were attacked by the unfamiliar disease of "berrugas" at the village of Coaque in Ecuador. Just what this disease was is uncertain, but it is the earliest scriptural record which can be construed to refer to verruga.

The anemic form of the disease apparently attracted little attention until much later, probably because to inspection alone it offered a less distinctive appearance. However, in the late 19th century it was noted that the soldiers who accompanied ore shipments from the mines at Cerro de Pasco to the coast became ill. Many of these guards were Negroes and when, as a contemporary observer put it, the blacks became whites, it was a matter of note.

Medical attention was definitely focused on Oroya fever in 1870 with the outbreak of an epidemic attending the building of the railroad from Lima to Oroya. Deaths among the personnel have been estimated at 7,000 and the epidemic made such an impression on the populace that the saying arose that every cross-tie on the railroad had cost a human life. The nature of the disease was obscure and it was called Oroya fever, although, as a matter of fact, the disease is not contracted in nor endemic in the city of Oroya itself.

The bond between Oroya fever and verruga peruana had not yet

received much consideration. Then, in 1885, Carrión performed the experiment which cost him his life, earned him medical immortality and by giving powerful impetus to the concept of a unitarian etiology profoundly influenced all subsequent thinking on the subject of Bartonellosis.

Daniel A. Carrión was a Peruvian medical student of an inquiring turn of mind who had spent much time studying verruga. He was dissatisfied with the knowledge available and in order to fill certain lacunae resolved to reproduce the disease in himself. He addressed his medical friends and requested them to inoculate him with verruga material. This they agreed to do, but only, according to Carrión's diary, after he had spent some time overcoming their objections. Perhaps his friends were right. After a 21-day incubation period he became ill, the illness progressed very rapidly and it soon became clear that the disease was not verruga. Carrión diagnosed it as Oroya fever, and this result was a complete surprise to him. Unfortunately, after 18 days of illness he died.

It seems clear that, following an inoculation of verruga material, Carrión died of Oroya fever. The conclusion widely drawn was that he had demonstrated the common etiology of the two conditions. The conclusion happened to be correct so that its influence was beneficial.

The causative organism was described in 1905 by the Peruvian physician, Barton, but was not generally accepted as such until the investigations of the First Harvard Expedition were published in 1915.

This report established Barton's bodies as independent organisms, named and gave a full description of them, described the pathognomonic lesion in which they are found in Oroya fever and concluded that they were indeed the etiological agent of this condition.

The cause of verruga was still obscure and it was not until Noguchi and Battistini in 1926 cultivated the organism that the solution was in sight. With this method it was possible to obtain cultures from Oroya fever patients. With these cultures verrugas were produced in monkeys and within the verruga an organism could both be seen and grown which was consistent with that inoculated and with that occurring in human verrugas. Although Noguchi's results were not fully confirmed from other laboratories, the findings of the 1937 Harvard Expedition to Peru supported those of Noguchi, and the unitarian view now seems to be proved beyond any doubt.

In the years 1928-31 Noguchi, Shannon, Battistini and others pro-

duced evidence incriminating the sand-fly, *Phlebotomus*, as the natural vector. This evidence Hertig has recently confirmed, extended and corrected.

So much then for the history of the disease, which indicates to us the long period required to individualize the syndromes, to establish their common cause and to indicate the mode of transmission.

Before proceeding further, a few words on terminology may be useful. Bartonellosis is used tonight to indicate infection with *Bartonella bacilliformis*. This can be followed by a disease known as Carrión's disease in one of its two manifestations. Oroya fever or Verruga peruana, or, again, no disease may ensue from the Bartonellosis and the infection remains asymptomatic.

The disease occurs in endemic foci in South America only, so far as we know. There, it is limited to the western part being found in certain valleys in the central and western Cordilleras of the Andes chain, between 13° South Latitude and about 4° North of the equator, that is about a thousand miles, comprising parts of Peru, Ecuador and Colombia. Peru is of course one of its strongholds and my own investigations were pursued there as a member of the 1937 Harvard Expedition to Peru, in the hospitals and institutes of Lima where, although the disease is not endemic, many patients are to be found, as well as in the nearby Rimac and Santa Eulalia valleys. It is a pleasure to recall the courtesy and complete cooperation of Doctor Telémaco Battistini through whom facilities for our work were obtained.

In Peru, the type of valley in which the infection prevails is peculiar and has even received the special name of "quebrada." As you may see, they are rather steep and narrow, dry and barren on the sides and tops with vegetation occurring chiefly along the stream bed at the base. But in these valleys there is an additional limit to the disease, it is found only at moderate altitudes. Thus, from sea-level to about 2400 feet the valleys are safe, from 2400 to about 8000 feet the disease is endemic and above 8000 the disease is not contracted. This limitation, we may point out now, is due in turn to the limitation of the insect vector *Phlebotomus* and is subject to some fluctuation according to the season, temperature, humidity and other conditions. Such then is the character of the endemic zone.

As concerns the disease, after a variable incubation period, which is often about three weeks but may be much longer, the initial symptoms

of pain and fever appear. The pains are characteristically those of the bones, joints, and muscles, they are intermittent, often occurring at daily intervals and variable in intensity. The fever may accompany the pain. It is likewise intermittent and variable. It is often mild, not rising above  $100.5^{\circ}\text{F}$ , but on first appearance it may be as high as  $104^{\circ}\text{F}$ , and when accompanied by chills and sweats quite resembles malaria.

This resemblance becomes embarrassing in the case of actual carriers of malaria who are frequent in the region. But the origin of the patient is a clue, as are the pains, quinine is ineffectual, and cultures for *Bartonella* will probably be positive. Actually, diagnosis is rarely made at this time.

From this stage the patient develops, in a period varying from some days to many months, one of the two classical types of Carrión's disease. For convenience and clarity the two will be described separately.

Your Oroya fever patient usually strikes you as being a very sick man when first seen, within a few days you are amazed that he is alive at all. The blood count can fall with startling rapidity and counts of 1,000,000 four days after the apparent onset are recorded. In all severe cases the count is 1,000,000 or below. Even with counts as low as these, the outcome is not necessarily fatal. In one of the patients whom I have seen, the count was 750,000. After some days at this level it began to climb slowly and a few weeks later was near three millions. This patient was apparently on the way to recovery but later died from an intercurrent infection.

The physical examination is not very revealing and the most characteristic finding is the generalized enlargement of the lymph nodes.

The symptoms derive for the most part from the anemia and its effects. The pains and fever of the preceding period intensify but are overshadowed by the rapidly progressing oligocythemia. Pallor is of the most extreme degree, save when mixed with icterus. Vertigo is at first caused by slight movement, soon the same stimulus causes syncope. At night, attacks of pain, fever and delirium render sleep difficult and fitful. Soon, prostration becomes marked and the patient, avoiding all motion, not only from weakness but to lessen pain and faintness, remains in a curiously fixed statuesque position. Finally, with an extreme degree of exhaustion and notable apathy, he awaits the outcome, which is usually evident in from 3 to 5 weeks.

At the time of marked anemia the parasites become numerous in

the blood, and there is a rough proportionality between the degree of the anemia and the number of parasites. More than 90 per cent of the red cells may be parasitized when the count is 1,000,000, whereas bartonellae are rare with a count of 4,000,000. Their appearance is distinctive, and no other human parasite resembles them even slightly. They are stained well by the usual blood stains and then appear as red-violet rods or coccoids situated upon the erythrocyte. They often occur in chain formation suggesting segmentation, and the elements of the chain frequently are at angles with one another giving rise to a V, Y or bayonet appearance. In intense infections they also occur within circulating monocytes and we shall see that they are also to be found in great numbers in the fixed phagocytes of the reticulo-endothelial system.

The other features of the anemia are that it is macrocytic, that the hemoglobin is less reduced than the red cells, giving a color index greater than 1, and that the hemoglobin content of the individual red cell is less increased than its volume, thus qualifying the anemia as hypochromic. Reticulocytes are abundant, in severe cases they may constitute 70 per cent of the red cells. As might be anticipated, liver therapy causes only a slight increase. The blood bilirubin is often, but by no means uniformly, increased. Neither hemolysins nor agglutinins have been found in the serum. There is no hemoglobinuria and, peculiarly enough, all searches for hemoglobinemia have been negative.

In fulminating cases death may occur in 10 days, but the more usual duration of fatal cases is about 3 to 4 weeks. Recovery is usually indicated by an abatement in the fever and a decrease in the number of bartonellae, the red count stabilizes at first, then increases to approach normal values at the end of about six weeks or so, when convalescence begins.

*But*, the disease almost *never* terminates with the convalescence, and when it does so, this is unpredictable. In the ordinary recovered case, Oroya fever is followed at the end of a variable period, often of about a month, by an attack of verruga peruana.

The prognosis in Oroya fever is not good. About 40 to 50 per cent of the patients may be expected to die, perhaps more in the epidemics. Remissions in the anemia are of favorable import but not invariably so, since relapses occur. It is generally believed in Peru that an abundant florid eruption of verrugas is almost invariably followed by recovery.

The diagnosis of Oroya fever presents no great difficulties when parasites are visible, which they usually are in critical cases. At other times, cultures should be made and the impetus to make them will be received when knowledge of prior residence in the endemic zones, and the history of fever and pain have been obtained.

The microscopic pathology of Oroya fever is just as distinctive in its way as are the parasite and the disease. To my knowledge, there is no other condition in man which gives a similar appearance. If any of you have encountered similar conditions, I should be very glad to learn of it.

At the post-mortem examination, the bodies of Oroya fever patients are of course pale and often somewhat yellow. But what is striking, after the opening of the cadaver, is the enlargement of lymph nodes which has already been noted at the physical examination. These are particularly noticeable in the abdominal cavity but the superficial groups are also involved. Cecal and retroperitoneal nodes of our patients reached 2.5 to 3 cm in length. These nodes are frequently hemorrhagic and the cut surface shows small areas of red and sometimes of yellow mottling. It is these nodes which present the peculiar microscopic appearance to be described later.

Petechial hemorrhages are rather widely disseminated and thus seems to be another of the usual findings. They occur in the skin and conjunctivae, on the surface of the heart, in the pleura and in the lung.

The spleen is frequently normal in size but may be enlarged. Lesions proving to be infarcts are often found. They are yellowish gray or white, are wider at the periphery of the organ than toward the center, are not distinctly wedged-shaped, measure about 1-2 cm at the surface and extend about 1 cm into the organ. The liver is more often enlarged than the spleen and usually appears normal even when conspicuous microscopic lesions are present.

The gross pathology is not particularly distinguishing, but when we turn to section material our attention is attracted at once by a unique appearance. This is constituted by the intracytoplasmic development of masses of *Bartonella* within the lining cells of the blood and lymph capillaries. This growth reaches an extreme degree, causes the cytoplasm to expand many times its normal width and then to bulge into the lumen of the vessel. Such distended cells are easily visible in stained sections with the low powers of the microscope. They resemble, at a hasty

glance, nothing quite so much as the endothelial cells during the extreme phagocytosis following blockade of the reticulo-endothelium

The infected cells are those usually classified as phagocytic endothelium. In addition, heavy infection was noted in the capillaries of the cortical region of the kidneys. The lymph nodes are most often involved but infected cells have also been found in the liver, bone-marrow, spleen, kidney, adrenal, pancreas and occasional cells in the heart and lung.

In one of these patients autopsied by Henry Pinkerton and myself, infected cells were found just below the epidermis and were surrounded by numerous newly formed capillaries and a few proliferated endothelial cells. These last two findings—newly formed capillaries and proliferated endothelial cells—are characteristic of the verruga state of Bartonellosis, while the infected swollen vascular lining cells are the earmark of Oroya fever. To find them associated is of interest, since it indicates what is probably the transition between the two very distinct pathological appearances.

In Oroya fever, within the infected cell the entire cytoplasm may be filled with parasites. The distribution is usually not uniform, for bartonella tends to form rounded masses or clumps. Within Kupffer cells of the liver there is less of a tendency to clumping and the majority of infected cells may show discrete organisms only. While the nuclei are at times obscured and distorted by masses of parasites which may lie upon the nuclear membrane, bartonellae have not been observed in a distinctly intranuclear position.

The lesion was absent in one of our patients who, after recovery, died later of toxoplasmosis, but was present in two others who died of Oroya fever. Our data and evidence in the literature suggest that it is only when the blood infection is heavy that the stuffing of the endothelial cells occurs.

Other lesions which have been found are less distinctive, in the lymph nodes and spleen, infarcts have been observed. It is thought that these follow upon vascular occlusion by the swollen endothelium. In the liver, although we did not observe it, areas of necrosis localized about the central veins have been reported. The bone marrow shows signs of energetic hematopoiesis.

The pathogenesis of the anemia is not well understood in its details. All of the evidence suggests that increased erythrocyte destruction occurs, but the mechanism producing the blood loss is obscure. Notably,

no lytic substances have been demonstrated either *in vivo* or in cultures. The bone marrow is very active, the reticulocyte count high and poor hematopoiesis cannot be invoked, save in a few cases and these appear to be secondary to the blood loss.

Very unfortunately animal experimentation is of little aid to us in connection with this problem, since Oroya fever can be reproduced only incompletely in an occasional *rhesus* monkey, and yet this animal, unsatisfactory as it is, is the best which is known. This again is inexplicable at present, for in the *rhesus* monkey, the verruga form of the disease caused by the very same organism can be reproduced at will.

Such then is Oroya fever which we may now define as a febrile anemia of rapid evolution and high mortality caused by *Bartonella bacilliformis*, and characterized pathologically by the distension of vascular endothelial cells with masses of parasites.

If the patient recovers from Oroya fever it is usually only to be attacked by the disease in its other form, verruga peruana, which we will now consider.

A patient with a profuse florid eruption of miliary verrugas is an unforgettable sight. Imagine, if you will, a person studded over with innumerable cranberries, the "berries" varying in color from red to purple, and you will gather what a very striking picture this is.

There is a considerable degree of variation and three types of verrugas are distinguished according to size and situation, miliary, nodular and "mulaire." The miliary type projects above the surface of the skin and is small, measuring about 1 cm. in greatest diameter. The nodular variety is more deeply seated in the skin and subcutaneous tissues, is larger, and does not at first project above the skin surface. It may, however, during the course of its evolution press against the skin and finally erode it, in which case it is known as a "mulaire" verruga from a resemblance to a lesion seen in mules.

The three kinds frequently occur together and since the eruption takes place by successive crops, verrugas of all types and at all stages of development and regression may be seen on the same patient.

The eruption occurs on covered and exposed areas alike. The regions of predilection are the limbs and face, they are rarer on the genitalia and scalp. They may occur on the mucosae and I have seen a patient with a profuse skin eruption present entirely analogous papules on the tongue and the roof of the mouth where they later become confluent.



However, the numerous reports in the literature of "internal verruga" occurring in the spleen, heart, brain, and other organs should be received somewhat critically, for there is no doubt that other lesions have been misdiagnosed as these internal verrugas.

The eruption persists from one month to two years. The milium lesions are the first to disappear, and unless infected leave no cicatrix, the miliary verrugas persist longer and with these, scar formation is the rule. The accompanying signs and symptoms are not conspicuous. There is some pain and fever and a moderate degree of anemia. The prognosis is good and uncomplicated verruga is very rarely fatal. Quite exceptionally Oroya fever may occur after verruga and carry off the patient.

A generalized well developed verruga eruption has an extremely distinctive appearance. The clinical diagnosis may be confirmed by the demonstration of bartonellae in the lesions and cultures from the blood are usually positive.

In sections there are three findings which typify the verruga: numerous new-formed small-caliber blood vessels, proliferated endothelial cells and *Bartonella*. The endothelial cells tend to occur in masses or islands lying in edematous connective tissue, the whole being infiltrated by a variable number of lymphocytes, plasma cells and polymorphonuclears. The bartonellae are conspicuous bright-red bacillary or granular structures when stained by the Regaud-Giemsa technique. They are situated in the neighborhood of, or within, endothelial cells. The formation of rounded masses of bartonellae within the vascular lining cells leading to distension of the latter, such as is seen in Oroya fever, is altogether uncommon in verruga.

With these three features in mind it should be possible to distinguish verruga from the majority of skin lesions with which it has been compared, such as secondary yaws, warts or molluscum contagiosum. The resemblance of verruga to telangiectatic granuloma is said to be striking, but bartonellae are not found in the latter.

The only real difficulty arises with an entity known as Bassewitz's tumors, also called "angiofibroma cutis circumscriptum contagiosum." This resembles verruga and in some cases objects which were called inclusions have been observed. It may be that some of these pseudo-verrugas really are verrugas and, if this is the case, then the geographic distribution of verruga may be far wider than we know it today.

Experimental verruga is easily produced in the rhesus monkey and

the lesion almost exactly reproduces the one seen in man. Successful inocula may be cultures, or verruga tissue, or tissue from Oroya fever. Inexplicably enough, blood, even when it contains enormous numbers of organisms and is injected in large amounts, will almost invariably fail.

These then are the two forms of Carrion's disease: verruga and Oroya fever. But in addition Bartonellosis may exist as an asymptomatic infection of no interest to the clinician perhaps, but of enormous importance epidemiologically. In the village of Callahuanca, where the disease is endemic, we undertook the first surveys to be made of the incidence of infection in the healthy population, using blood cultures for this purpose. You have seen the type of house which exists there, it seems almost incredible that sterile bacteriological work could be carried out in such surroundings. But so it turned out, our contaminations, surprisingly, were very low and we found that about 10 per cent of the population were carriers of *Bartonella*. Similar figures have since been obtained by others. From this and other data it appears that *man* is the chief reservoir of *Bartonella* and since these carriers are often perfectly healthy, probably the chief transporting agent as well.

Concerning *Bartonella bacilliformis* some data have already been presented. The organism bears a resemblance to the *Rickettsia* of epidemic typhus in its morphology and in its development within the cytoplasm of cells. *Bartonella*, however, can be propagated indefinitely in cell-free medium. The morphology in the blood has already been seen and it is here that variation is most marked, rods, coccoids and rings can all be observed, sometimes in the same patient.

The culture medium usually used is the semi-solid agar containing rabbit serum and hemoglobin employed by Noguchi and Battistini in their pioneer work in 1926. In this medium growth is apparent in 10 days or so in a zone approximately 1 cm wide which occurs about 1 cm below the surface.

Colonies may be macroscopic and appear as white rounded masses rarely larger than a millimeter in diameter, or the growth may be more scattered and appear as a faint halo. Growth is optimal at P H 7.8 and at 28°C. Of its metabolic activity in culture, the fact that it does not hemolyze red cells is perhaps the most interesting. In tissue cultures *Bartonella* develops within the cell cytoplasm and also extracellularly, in the insect vector the localization is not yet definitely known.

Some strains are motile and in connection with these, flagella have been described. There are no spores nor capsules. Reproduction takes place by binary fission and there is no evidence of a complex life cycle, such as once was considered evidence of the protozoan nature of *Bartonella*.

Bartonellosis is an insect-transmitted condition. The only proved vector is the sand-fly or *Phlebotomus*. In Peru it is the species *verrucarum* which is responsible and the peculiar epidemiological features of the disease are closely linked to the biology of *Phlebotomus verrucarum*. This fly measures about 5 mm in length. It is consequently quite small and will pass through the ordinary mesh mosquito netting. The raised position of the wings while at rest is quite characteristic. Being whitish in color and since it is seen chiefly at night, the term "ghost gnat" seems peculiarly appropriate. Only the female takes blood.

In the infected quebradas it is captured in the vicinity of human habitations. Like man, the fly fears excessive dryness and both animals therefore gravitate to the more humid areas near the streams at the bottom of the valley.

The old report that verruga is contracted only at night in Peru is substantially correct. These phlebotomus do not like light and are active only from dusk to shortly after sun-up. I, and a great number of other investigators have spent time in the verruga zone, restricting our visits to day-light hours without becoming infected. The fly can, however, be captured during the daytime by disturbing it in its natural hiding places, such as caves and rock crevices.

The limitation of the disease to moderate altitudes is correlated with the distribution of the vector. Above the upper limit, the night temperature seems to be too low for the fly. Below the lower limit, the humidity is probably not great enough. These data have been obtained in Peru where the most careful entomological investigations have been carried on.

On a basis of this information, the restriction of Bartonellosis to a limited area in South America was once explained, on the assumption that only Peruvian sandflies were good vectors. However, this assumption was gratuitous, being completely unsupported by experiment. In the late 1930's an epidemic broke out in Colombia which was finally identified by Dr. Patiño Camargo as Oroya fever. There, the epidemiology is similar to that occurring in Peru, and *Phlebotomus* has been

taken in the bartonella area. But from Colombia a fact of the very highest importance has been brought to light.

This is, that none of the phlebotomi incriminated in Peru has thus far been found, so that, although the common vector is not yet known, it seems altogether likely that it is not the same in Colombia as in Peru. From this we may conclude that *Bartonella bacilliformis* is not strictly limited in its insect host. This datum further suggests that the epidemic took place by the introduction of *Bartonella bacilliformis*, possibly through carriers, rather than by the acclimatization of infected foreign sandflies.

The question immediately arises as to the suitability of still other sandflies as vectors. Since the species of these insects which feed on man are widely distributed throughout the world in tropical and subtropical areas, the question is not without its importance. In the United States very recent investigations have shown that *Phlebotomus* is more widely represented than was known previously and at least one species, *Phlebotomus diabolicus*, found in Texas, is a known human feeder.

This question has, so far as I am aware, never been attacked experimentally. From our knowledge of the biology of *Bartonella bacilliformis* however, and by analogy with other insect-borne diseases caused by microorganisms, there is no reason to suppose that a number of species of *Phlebotomus* would not prove to be suitable vectors. Certainly the data obtained from Colombia support this view. And we also know that human carriers are capable of introducing *Bartonella* into hitherto uninfected areas.

Concerning the possibility of spread, there is then no reason for complacency. The factors which have limited the disease in the past appear to be first those natural environmental circumstances which have limited the distribution of phlebotomi and secondly the absence of mass movements of the infected populations.

Man very rarely found it possible or expedient to affect the phlebotomi adversely, although it should be admitted frankly that he has not expended any considerable effort in this direction. As a result of this attitude, it is probably true that human activities have tended, on the whole, toward extension of the disease where extension was possible by the introduction of carriers into phlebotomus-infected zones. We have depended, it might be said, on Nature to protect us and Nature is not obviously partial to the human species.

In closing this presentation concerning Bartonellosis, I note an oversight I have neglected to discuss the therapy of Carrión's disease. But this is readily summarized, no effective etiological treatment exists.

*African trypanosomiasis*, the second disease to be considered this evening, has had a most notable retarding effect on the development of Central Africa. If it be considered that the Continent was known before Western Europe had felt the impact of Roman civilization and that Carthaginian traders were active on the West Coast of Africa, one cannot fail to be impressed with the contrast between the present development of Central Africa and that say, of the Americas, discovered so many centuries later.

This retarded development recognizes many causes—climate, disease, etc. But the part played by the trypanosomiasis of man and animals—not only by decimating human populations but through epizootics which have rendered animal husbandry difficult or impossible—is not easy to over evaluate.

Even today, after many years of sustained effort directed against the disease, the morbidity it causes is still very considerable. Thus in Gambia in 1936, 40 per cent of the in-patients were affected with sleeping sickness, which caused 30 per cent of the hospital deaths. The total number of cases is unknown, but a recent report from the League of Nations states that 1,000,000 African natives are under treatment and it is scarcely possible to make even an estimate of the number of undiagnosed cases.

We in the Americas are certainly fortunate that the sleeping sickness has never taken a foothold here. The disease has been introduced and probably innumerable times, at the time of the slave trade, but has never become endemic. This, of course, was due to chance, not to foresight. It so happens that the only known vectors which allow the trypanosomes to go through their complete cyclical development are the tsetse flies of the genus *Glossina*, which now exist only in Africa.

However, such has not always been the case. At one time the tsetse fly existed in the United States, for fossils of a long extinct species have been found in miocene deposits in Colorado. That *Glossina* has died out in the Americas seems clear, why they died out is not so evident, and whether if re-introduced they would be able to acclimatize themselves is completely unknown. Among all these uncertainties, one thing, however, is known. *Glossina* has been transported by air to South Amer-

ica, since dead tsetse flies have been taken in the pools of insects obtained after fumigation of airplanes making the South Atlantic crossing

The possibility of the establishment of African trypanosomiasis in the Americas is remote. It will not take place from the introduction of infected individuals alone, it may take place should the flies ever become established and both flies and patients be present together

In Africa, the only continent where the disease exists, it is very widespread, extending roughly from Dakar in Senegal to Angola on the West Coast, and from the Southern Sudan through Rhodesia in the east

If the map be studied attentively, it will be noted that strongholds of the disease are found along the great river systems, the Congo and its tributaries, the Volta, and so on

This is so, because one of the chief vectors, *Glossina palpalis*, and some of the other vectors congregate along the rivers

I was given a beautiful demonstration of how water fits into the epidemiology of sleeping sickness at a village in the Kasai region of the Belgian Congo situated on a small river which was one of the tributaries of the Congo. The white planter had his home placed on a hill, less than a mile away from the river and almost never saw a tsetse fly there. He considered the risk so slight, that although he had invested in an electric generating plant, a frigidaire, etc., he had never considered it necessary to install screens

Yet, at the ford on the river, the glossinas were abundant. Now to travel from the village to the nearest city it was necessary to cross the river, which was done in a dug-out canoe, handled by a native ferryman. One was no more than a few feet out when the tsetses began to appear in great numbers. In the crossing, which took at the outside perhaps 5 minutes, at least a dozen tsetses attacked the white missionary seated in front of me. And on our landing on the opposite side we encountered masses of the flies. My companion, in a few minutes' time, captured a dozen on my back, and probably missed as many more, and all the while I was extremely active brushing still others off my sleeve, pant-legs, etc.

So much then for what the fly density may attain. It seemed perfectly clear that no one could spend any time at the river without undergoing the most serious risk of being bitten, even when clothed. But the natives, I remind you, were almost totally unclothed

And for the natives a great deal of their activities were carried on at

the water's edge. There they bathed, there the washing was done—the mothers taking the children along so they could watch after them—and there the villagers went for their daily supply of water.

So you had what was almost an ideal situation—epidemiologically speaking—for transmission. Infected persons, flies and non-infected individuals juxtaposed and the same circumstances repeating themselves over and over again at almost daily intervals. Cases of the disease were not yet frequent, but the local health officer feared, and I think quite rightly so, that an explosive outbreak might occur at any time.

It is frequently stated that the tsetse prefers black skins to white ones. From my experience this is no cause for easiness. Either the flies were misled by the dark color of my clothing, or their color perception was poor, but whatever the explanation, the continued attention of dozens of the flies was to me satisfactory evidence that the flies considered me as succulent a dish as was to be found in the neighbourhood.

My own recent experience with sleeping sickness was obtained as member of an expedition organized under the joint auspices of Harvard University and The American Foundation for Tropical Medicine. It derives chiefly from a stay in Liberia at the hospital of the Firestone Plantations Company at Harbel, where facilities were very kindly made available for my work, and from a visit to the Belgian Congo where an opportunity was offered to study a focus in the interior, and to become acquainted with the investigations carried out in the splendid central research Institute at Léopoldville.

Two of the signs and symptoms of sleeping sickness are conspicuous to everyone, the enlarged lymph nodes and the somnolence. By reference to these, some idea as to its history may be pieced together. As far as I have been able to learn, the earliest reference known is that of an Arab writer Al-Qualquashaudi, of the 14th century.

One strong impetus to its study was an economic one, and with the advent of the slave-trade it became realized—at least on the part of the shrewder traders—that natives with enlarged cervical nodes were a poor investment, since they were likely to die on the long trip across the Atlantic. It may well be that this clue was obtained from the Africans themselves, for in certain regions the natives practised extirpation of the enlarged nodes, apparently believing that the latter were the cause of the disease they accompanied.

From the middle of the 18th century on, various travellers mentioned

the disease and the name of one of these, Winterbottom, has been retained in the designation Winterbottom's sign, to denote the enlarged cervical nodes

One other of these travellers is of particular interest and that is the journalist Stanley On his famous trip in search of Livingstone, he organized his party, obtained his carriers, etc in West Africa, and then proceeded cross-continent to the vicinity of Lake Victoria By many authorities, it is believed that the natives he brought with him introduced the disease into Eastern Africa, giving rise to the terrible epidemics which in certain areas of the lakes region destroyed two-thirds of the population in eight years

The important scientific discoveries were not made until after Africa was carved up into its various colonies

In the 1890's Bruce showed that "nagana," an important disease of cattle and game, was caused by trypanosomes and carried by tsetse flies

Forde and Dutton in 1901 and 1902 observed a peculiar case of pyrexia in a resident of Gambia, studied him carefully and discovered trypanosomes in his blood The latter year Castellani observed trypanosomes in the spinal fluid of somnolent persons Some of these patients also had the organism in the blood, which indicated the bond between the febrile and the somnolent forms

The role of the tsetse, suspected by the natives, was proved by Bruce and Nabarro in 1903 However, it was not until the work of Kleine in 1912 that it was clearly realized that the trypanosomes underwent cyclical development in the tsetse, that during a period of their multiplication they were non-infectious, but after various structural changes finally migrated to the salivary glands, where as the so-called metacyclic forms they produced infection when injected by the bite of the fly

An early successful therapeutic agent was atoxyl, the pentavalent arsenical synthesized by Pasteur's great rival Béchamp Tryparsamide, synthesized by Jacobs and Heidelberger, and introduced into therapy by Louise Pearce, is an improvement and remains today one of the two standard drugs used in this disease

The other is a Bayer product, Bayer 205, known also as Antrypol and Naphuride This is a non-metallic drug similar to the benzidine dyes It is very effective in the early stages of sleeping sickness and has itself a highly interesting history, being one of the few drugs which has earned a place in politics as well as in therapeutics Its political status



came about as follows. The drug was produced after the last war and the Germans, knowing that they had something valuable, kept its composition secret. The reason for this was revealed when one of the men familiar with it gave an address, in which he stated that Bayer 205 was the key to the successful colonization of Africa, that its structure should accordingly be kept secret and the only price to be accepted for its revelation was the restoration of some of the colonies Germany lost during the last war. This plan was not successful, for although the Germans published enthusiastic reports on 205, the rest of the world wanted to test it themselves. Finally, in an impasse, the Germans furnished some for trial. A small amount came into the hands of the chemist Fourneau in Paris, who promptly synthesized it, published the formula and thus made it available to all.

In regard to the disease, the first symptoms may result from the infecting bite itself. I have only seen one such case. At the site of the bite a reaction was visible at the end of about 24 hours. It increased during the next 24 to 48 hours and then consisted of a reddened edematous area about 3 inches in diameter, slightly raised and hot to the touch, but not painful on palpation.\*

At this time trypanosomes could be found in the area by puncture. The lesion then regressed and at the end of a week was inconspicuous. It is said that this lesion may sometimes progress, become necrotic and persist for a long while.

From the time of the infecting bite a variable period intervenes before complaints are voiced. In Liberia, where the disease seems mild in type, this period may extend over several months and many of our patients were picked out because of enlarged lymph nodes when they stated that they felt perfectly well. Elsewhere, the progress is more rapid and fever is noted at the end of a few weeks.

The fever may be intermittent or remittent, but characteristically is very irregular. It is said to be more common in whites. The pulse is rapid and remains so during apyretic periods.

The enlargement of the lymph nodes is a sign of more frequent occurrence. It rarely reaches the pigeon egg size, which, because of its photogenic qualities, is so often used in illustrations, and the nodes are more often about 1 cm or 15 mm in greatest dimension. They are at first soft and succulent, later becoming hard and fibrous. Winterbot-

toni's sign consists in the swelling of the posterior cervical nodes, the epitrochlears and supraclaviculars are also often enlarged. These swollen nodes frequently contain trypanosomes, particularly at the soft and succulent stage, and puncture of these nodes is one of the principal methods of diagnosis.

Skin eruptions are said to be frequent in whites. My patients were all negroes and I did not observe any skin eruptions. Pruritus was common, and is described in sleeping sickness, but it was difficult to assign its true cause, since a dermatitis, a form of crawl-crawl, believed to be caused by chronic infection with the itch-mite, *Sarcoptes scabiei*, was almost universal. Edema of the face or of the eyelids or about the hands, feet and joints is common.

Such then are the signs and symptoms of the early stage of sleeping sickness. At this time trypanosomes may be found in the blood and lymph nodes, they usually are absent from the spinal fluid. Treatment instituted at this period has a good chance of success, later the prognosis is much more dubious.

From this stage the patient gradually passes into the period of nervous involvement.

Changes in the sleep pattern occur early. At first it may be nocturnal insomnia with diurnal somnolence, and be somewhat difficult to assign to its true cause. Deep hyperesthesia is frequent, and the turning of a key in a lock may give rise to a pain which is hardly bearable.

Then, as time progresses, in periods varying from a few months to a few years, the disease evolves and the patient presents the classical picture of sleeping sickness. He is dull and apathetic, he comprehends poorly, he is disinclined to exertion and frequently goes to sleep even in the sunlight, and this sleepiness so masters him that he fails to awake even for the necessities of food and cleanliness.

Upon examination, tremors of the tongue and fingers are frequently noted. The gait is peculiar, often with shuffling, but in general there is no paralysis. There may be clonus of the ankle or patella. Romberg's sign is frequently positive. Headache is a common complaint and frequently psychical changes manifested by delusions, hysteria and attacks of mania are noted.

As the disease progresses, these symptoms become more marked, emaciation of extreme degree will occur if excellent nursing does not prevent, bedsores form, the blood pressure falls and the patient passes

away in coma

The duration of the cerebral stage is from a few weeks to a few years

These symptoms are frequently dissociated I recall distinctly a woman with trypanosomes and over a thousand cells in her spinal fluid, who was bright, alert and responsive She did not sleep very much and gave no evidence of any psychical disturbance She did have hyperactive reflexes, an ankle clonus and Romberg's sign, so that her complaint was that she walked badly Since I was interested in evaluating a hitherto unused drug, this patient seemed a most interesting case to try it on But to my great disgust, after the treatment was only half completed, her walking had so improved that she left the hospital and walked home

The elements of the clinical diagnosis have already been given Trypanosomes are found in the blood and lymph nodes in the early period, and since either may be negative, both should always be examined In the cerebral stage the parasites occur in the spinal fluid, but usually only after a significant rise in the cell count

If all these examinations are negative, the inoculation of guinea-pigs and rats may be essayed—it may, however, often be negative with strains of low virulence such as are found in Liberia

Cultures, in which I am particularly interested, may be resorted to, but they are not yet suitable for routine use

The earlier the diagnosis can be established, the better the prognosis Treatment initiated in the early stages often cures the patient, in the cerebral stage not only are the trypanosomes more difficult to eradicate, thus requiring higher doses—a decided drawback with a toxic drug—but if tissue damage is too marked, it may not be possible to restore normal function Untreated cases almost always die, although there are some reports of spontaneous cures As pointed out before, there are variations in the severity of the disease in different areas

I was not able to obtain any autopsy tissue in Liberia, and the following pathological account is based on the reports of others

Lesions of the lymph nodes and the central nervous system are those most constantly observed The lymph nodes are enlarged, particularly those in the posterior cervical, epitrochlear and supraclavicular regions Microscopically, the follicles appear enlarged and an infiltrate is present composed of polymorphonuclear and plasma cells At times the so-called 'morula cells,' to be discussed subsequently, may be found Later the

nodes become sclerotic and there is marked growth of connective tissue

The brain is the site of a widespread encephalitis, found in both the white and grey matter, with extremely marked infiltration around the vessels. This perivascularitis is distinguished by the predominance of plasma cells which is said to be greater than that observed in any other infection. In addition to plasma cells the infiltrate is said to be composed of neuroglial and microglial elements mixed with macrophages of meningeal and monocytes of vascular origin. The vessels themselves show some swelling of the endothelium, but no endarteritis or thrombosis.

In addition to the perivascular infiltration, the presence of the so-called "morula cells" of Mott in considerable numbers is characteristic. These are derived from plasma cells and are now thought to be identical with Russell bodies, which they very much resemble. Accordingly, while they are characteristic of sleeping sickness, they are no longer thought to have any specificity.

The meninges are sometimes thickened and usually show a widespread perivascular inflammatory lesion similar to that described in the brain.

Trypanosomes can be demonstrated in sections after fixation with alcoholic sublimate and staining with Giemsa's solution according to Wolbach's technique. For certain authors the organisms are present in the brain and with sufficient constancy to suggest a direct cause and effect relationship to the lesions, but this is by no means a universally held opinion. The problem does not appear to have been studied very exhaustively in man, and it would seem that here is a situation where collaboration between microbiologists and neuropathologists might be fruitful.

The trypanosomes of African sleeping sickness are flagellate organisms readily detectable in blood or lymph node fluid by their active movements.

The only human parasite with which they are likely to be confused is *Trypanosoma cruzi*, which causes the so-called "American trypanosomiasis," or Chagas' disease. But *Trypanosoma cruzi* is morphologically different, has an intracellular tissue stage in man, is readily cultivated and has a quite different vector.

The African trypanosomes readily become arsenic-fast and it is known that this drug resistance persists after passage through the fly.

It is easily understood therefore how an arsenic-fast strain may be found in certain areas, and accordingly why dosages of arsenicals used in treatment may vary considerably from one region to another

An interminable, and to my mind tiresome and fruitless discussion has been carried on for years as to whether more than one species of trypanosome is involved in sleeping sickness. Everyone agrees that *Trypanosoma gambiense* is a good valid species, but they are not agreed about *Trypanosoma rhodesiense*, which does differ biologically, but not morphologically. Since there is no common agreement amongst protozoologists as to the validity of biological species, the discussion is likely to rage unabated indefinitely. It may be noted, however, that the unicists do not push their argument to the logical extreme and identify the human trypanosomes with a morphologically indistinguishable organism *Trypanosoma brucei*, which does not infect man. They are right, it seems to me, on a basis of convenience, and for the same pragmatic reason I believe *Trypanosoma rhodesiense* should receive a separate designation, whether that be of specific rank or not, is of far less importance.

The epidemiology of the disease involves chiefly man and the fly. Man is the important reservoir of the infection; it seems, wild animals, such as the sitatunga antelope (*Tragelaphus spekei*), playing a subsidiary role in this respect. However, the fact that a domestic animal, the pig, may harbor the infection and be capable of infecting flies, is of considerable interest in those regions where hog-raising is common.

Wild animals do play a part in furnishing nourishment to the flies which are quite catholic in their tastes. Many authors, impressed with this fact, have proposed widespread destruction of game to control the flies, but, in the absence of protection of man, this measure may have just the contrary effect from that intended.

The anti-fly measures which have been used are innumerable, and it would seem that almost no method was too fantastic not to have had some proponents. The great Robert Koch, for example, impressed with the fact that *Glossina* would feed on crocodiles, proposed the systematic destruction of crocodile eggs as a means of controlling the flies in Africa.

Actually the methods in use have to vary according to the *Glossina* they are directed against. While a number of species are good vectors, they can be classified roughly into the hygrophile group exemplified by *Glossina palpalis*, which is found in the vicinity of water, and the

verophile group, such as *Glossina morsitans*, which can live under much drier conditions

Clearing vegetation along river banks, particularly at fords, village sites and other places of congregation has proved effective against *Glossina palpalis*. Against the forest and savannah species, resettlement of villages in burned over areas, which are subsequently put under cultivation, has been beneficial.

For the protection of the individual, a development in the last year is of more promise than anything which has happened in a very long time.

This is a method of chemo-prophylaxis originated and now under study in the Belgian Congo. van Hoof and his collaborators studied the effect on African trypanosomiasis of Pentamidine, a new drug now coming into use in kala-azar. In *treatment* it was not superior to drugs already in use. But carrying their experiments further, they noted that in animals, single injections would confer protection against the fly-borne disease, this protection extending over many months.

The method was extended to man, first with laboratory experiments on two volunteers. These men received a single intramuscular injection of Pentamidine and then infected flies were fed on them every 2 or 3 days for about a year, until the men became positive. This took 295 days for one man, the other did not become positive until 12 months after the injection. Both of these men were blood positive, the cerebro-spinal fluid was examined in one at the end of the experiment and found normal.

At the time I was in the Congo, that is, in June, the early results of the first field trial were known. The results indicated that protection was obtained from a single injection of 2 to 3 milligrams of Pentamidine per kilogram of weight for a period of 6 months. Given intramuscularly, the drug was not notably toxic and the protective results obtained were markedly superior to those given by Bayer 205.

The method is too new as yet, and has been tried on too few people for any firm conclusion to be drawn as to its value. But should the promise of effective mass prophylaxis, following a single injection every six months, be kept, it may well change the whole complexion of the sleeping sickness problem in Africa.

Another recent discovery of interest is that pyrethrum is an effective tsetse repellent. A preparation in a vanishing cream base prevented

tses from biting for periods varying from 2 to 6 hours, depending on the rate of perspiration. Repellent is perhaps not quite the right word, for the flies alighted readily enough, but did not take blood. Pyrethrum, it thus seems, can be of service in individual prophylaxis.

The treatment remains what it has been for some time. Bayer 205 and tryparsamide, given either separately or more often nowadays, in succession. The usual treatment consists of a course of Bayer 205 to total 10 grams, 1 gram being given intravenously once or twice weekly. Then after a two-week rest tryparsamide is administered—1 gram the first dose, then 2 grams, once or twice weekly to total 15 to 25 grams, or more, depending on the response.

New developments in therapy comprise several arsenical compounds which now past the experimental stage, have been tried clinically. One of these is Melarsen oxide, a trivalent arsenical compound. The initial results which my patients showed were encouraging, the drug is effective in both the blood and cerebral stage and appears to be relatively non-toxic. But in a chronic disease, such as trypanosomiasis, results can only be judged after years of careful study, and whether Melarsen oxide presents advantages over drugs now in use, is not yet known.

The amidine compounds are being used prophylactically as I have described, their use in therapy is on the wane.

As for penicillin and the sulfonamides, unfortunately sleeping sickness is one of the diseases in which they have produced no spectacular effect.

In closing, I wish to express the hope, that by pointing out certain unsolved problems in the two diseases discussed tonight, that this presentation may serve in some sort as a stimulus to the investigation of those tropical conditions which soon now will come to your notice.

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